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(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors: CARRUTHERS, Nicholas, I.; 358 West End Avenue, North Plainfield, NJ 07060 (US). ALAIMO, Cheryl, A.; 218 Onizuka Court, Somerset, NJ 08873 (US).

(74) Agents: BOXER, Matthew et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

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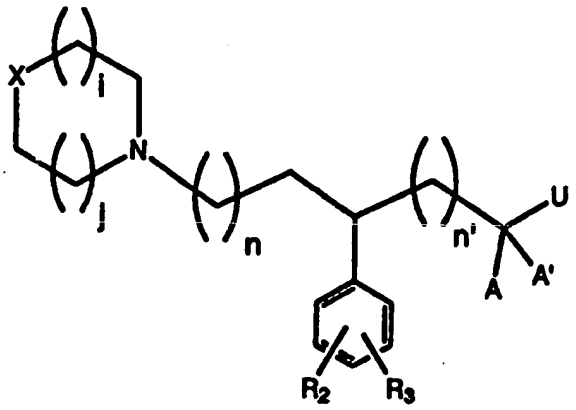
(54) Title: PIPERIDINE DERIVATIVES AS NEUROKININ ANTAGONISTS

(57) Abstract

The invention relates to compounds of formula (I), wherein X, i, j, n, n', A, A', R_2, R_3, and U are as decribed herein. The compounds of the invention are NK_1 or NK_2 or NK_3 receptor antagonists and as such are useful in the treatment of diseases such as asthma.



(I)

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PIPERIDINE DERIVATIVES AS NEUROKININ ANTAGONISTS

BACKGROUND OF THE INVENTION

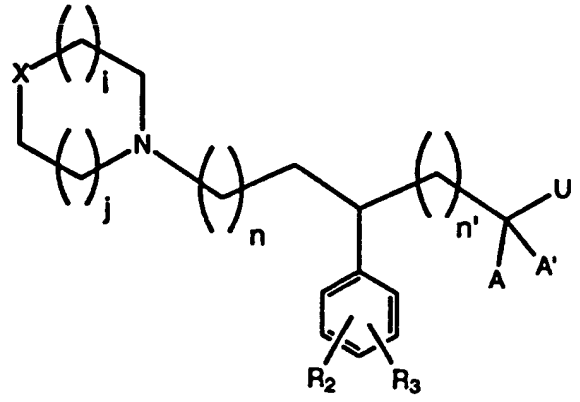
The present invention relates to a genus of compounds useful as antagonists of neurokinin receptors. In particular, these can be neurokinin-1 receptor (NK_1) antagonists, neurokinin-2 receptor (NK_2) antagonists, and neurokinin-3 receptor (NK_3) antagonists,.

Neurokinin receptors are found in the nervous system and the circulatory system and peripheral tissues of mammals, and therefore are involved in a variety of biological processes. Neurokinin receptor antagonists are consequently expected to be useful in the treatment or prevention of various mammalian disease states, for example asthma, cough, bronchospasm, inflammatory diseases such as arthritis, migraine, nociception, and various gastrointestinal disorders such as Crohn's disease.

In particular, NK_1 receptors have been reported to be involved in microvascular leakage and mucus secretion, and NK_2 receptors have been associated with smooth muscle contraction, making NK_1 and NK_2 receptor antagonists especially useful in the treatment and prevention of asthma.

Summary of the Invention

The invention relates to compounds of the formula



I

wherein each i and j is independently selected from the group consisting of 1 and 2;

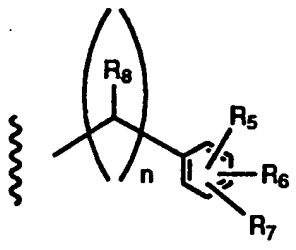
each n is independently selected from the group consisting of 0, 1, 2 and 3; and each n' is independently selected from the group consisting of 1, 2 and 3;

wherein A and A' are H, or A and A' taken together are =O, =S; or =N-R_4;

X is selected from the group consisting O, CO, C(R, R_1), C=C(R_1,R_8), NR_1, and $S(O)_e$ wherein e is 0, 1, or 2;

R is selected from the group consisting of H, OR_8, $CON(R_8)_2$, CN, $S(O)_eR_8$, $SO_eN(R_8)_2$, CO_2R_8, and NR_4COR_8;

R_1 is selected from the group consisting of H, (C_1-C_6)-alkyl (C_3-C_8)-cyclo-alkyl,



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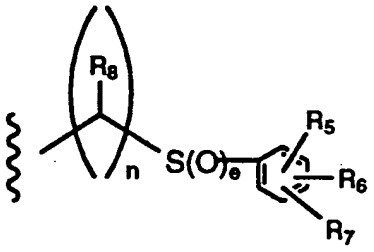


;

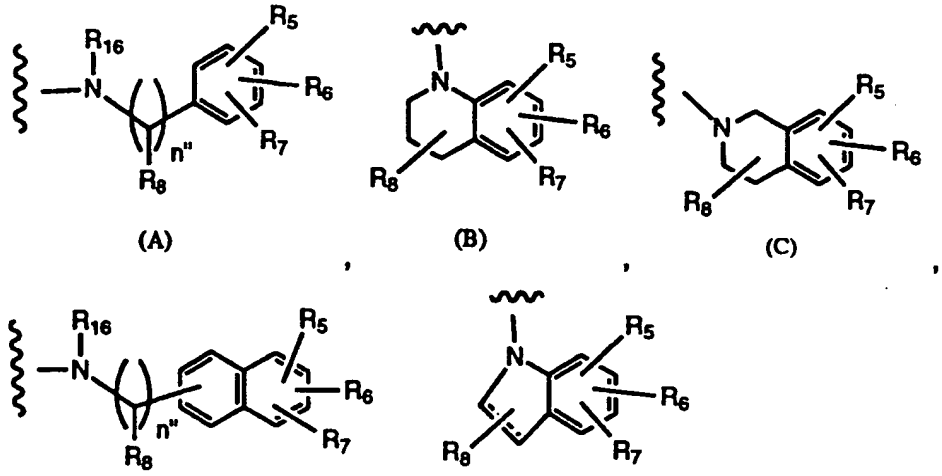
R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, halogen, (C_1-C_6)-alkyl, CF_3, C_2F_5, OR_8, COR_8, CO_2R_8, $CON(R_8, R_8)$, $N(R_8, R_8)$, $N(R_8)COR_8$, $S(O)_eR_8$, $OC(O)R_4$, $OC(O)N(R_8, R_4)$, $NR_8CO_2R_4$, $NR_8(CO)N(R_8,R_8)$, R_{15}-phenyl, R_{15}-benzyl, NO_2, $NR_8SO_2R_4$, $-S(O)_2N(R_8)_2$ or when R_2 and R_3 or any two of R_5, R_6 and R_7 are on adjacent carbons they may form a $-O-CH_2-O-$ group;

each R_4 is independently selected from the group consisting of alkyl, substituted alkyl, substituted aryl, and substituted benzyl;

each R_8 is independently selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, and substituted benzyl;

each R_{15} is independently H, halogen, lower alkyl, lower alkoxy; and

U is



, or

n" is independently selected from the group consisting of 0, 1, 2 and 3;

the dashed line is an optional carbon-carbon bond;

R_{16} is H, $(C_1$-$C_6)$-alkyl, $-S(O)_2R_4$, COR_8, CO_2R_4, $CON(R_8)_2$, R_{15}-phenyl or R_{15}-benzyl.

Substituted means substituted with a substituent selected from the group consisting of H, $(C_1$-$C_6)$ alkyl, OCF_3, CF_3, and C_2F_5.

Also preferred are compounds of formula I, wherein i is 1 and j is 1.

Also preferred are compounds of formula I, wherein n is 1, n" is 0, 1, or 2, and n' is 1.

Also preferred are compounds of formula I, wherein n, n' and n" are all 1.

Also preferred are compounds of formula I, wherein n and n' are both 1 and n" is 0.

Also preferred are compounds of formula I, wherein n and n' are both 1 and n" is 2.

Also preferred are compounds of formula I, wherein A and A' are both H.

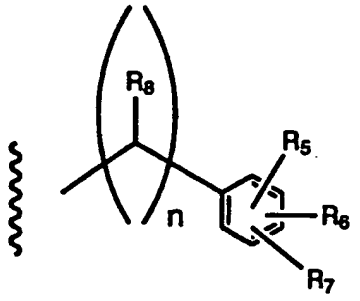
Also preferred are compounds of formula I, wherein A and A' taken together are =O.

Also preferred are compounds of formula I, wherein X is C(R, R_1).

Also preferred are compounds of formula I, wherein R is OR_8, $CON(R_8)_2$, CN, or NR_8COR_8.

Also preferred are compounds of formula I, wh rein X is NR_1.

Also preferred are compounds of formula I, wherein R_1 is



Also preferred are compounds of formula I, where n is 0 or 1 and R_8 is H.

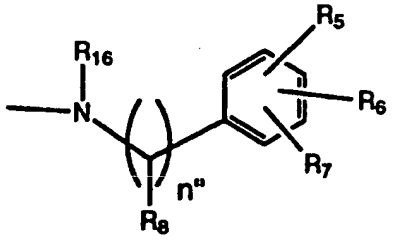
Also preferred are compounds of formula I, wherein R_2, R_3, R_5, R_6 and R_7 are H, halogen, C_1-C_6 alkyl, CF_3, OR_8, COR_8, CO_2R_8, $CONR_8R_8$, or NR_8R_8

Also preferred are compounds of formula I, wherein R_{16} is H or alkyl .

Also preferred are compounds of formula I, wherein each R_8 is H, C_1-C_6 alkyl, or R_{15}-phenyl

Also preferred are compounds of formula I, wherein R_8 is H or substituted alkyl.

Also preferred are compounds of formula I, wherein U is



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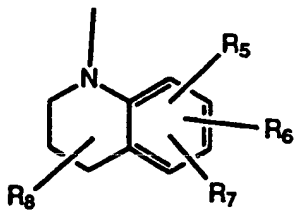

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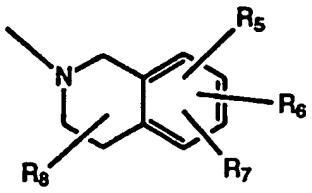

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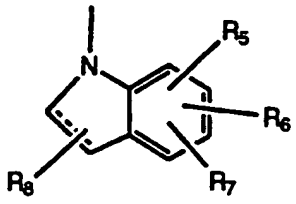
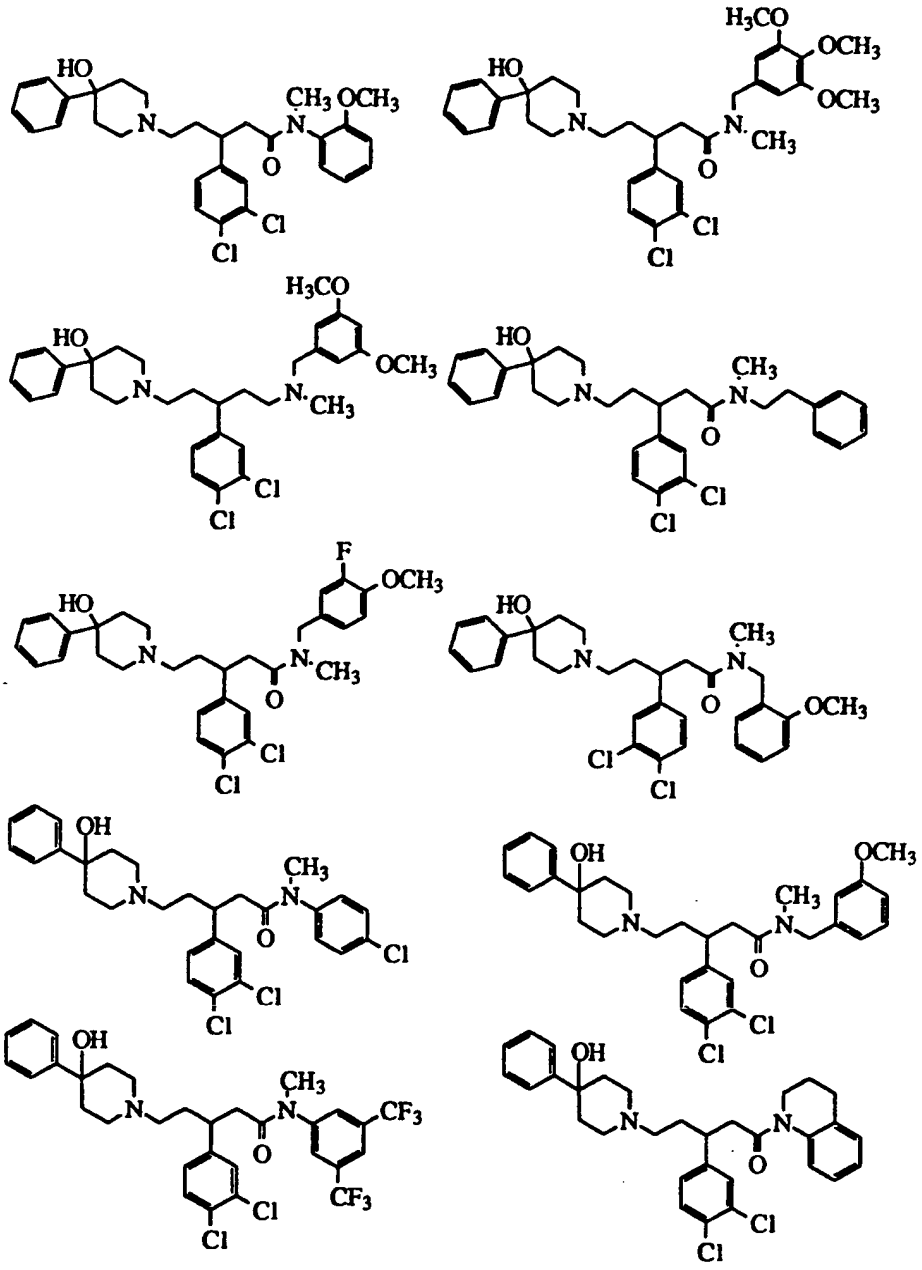
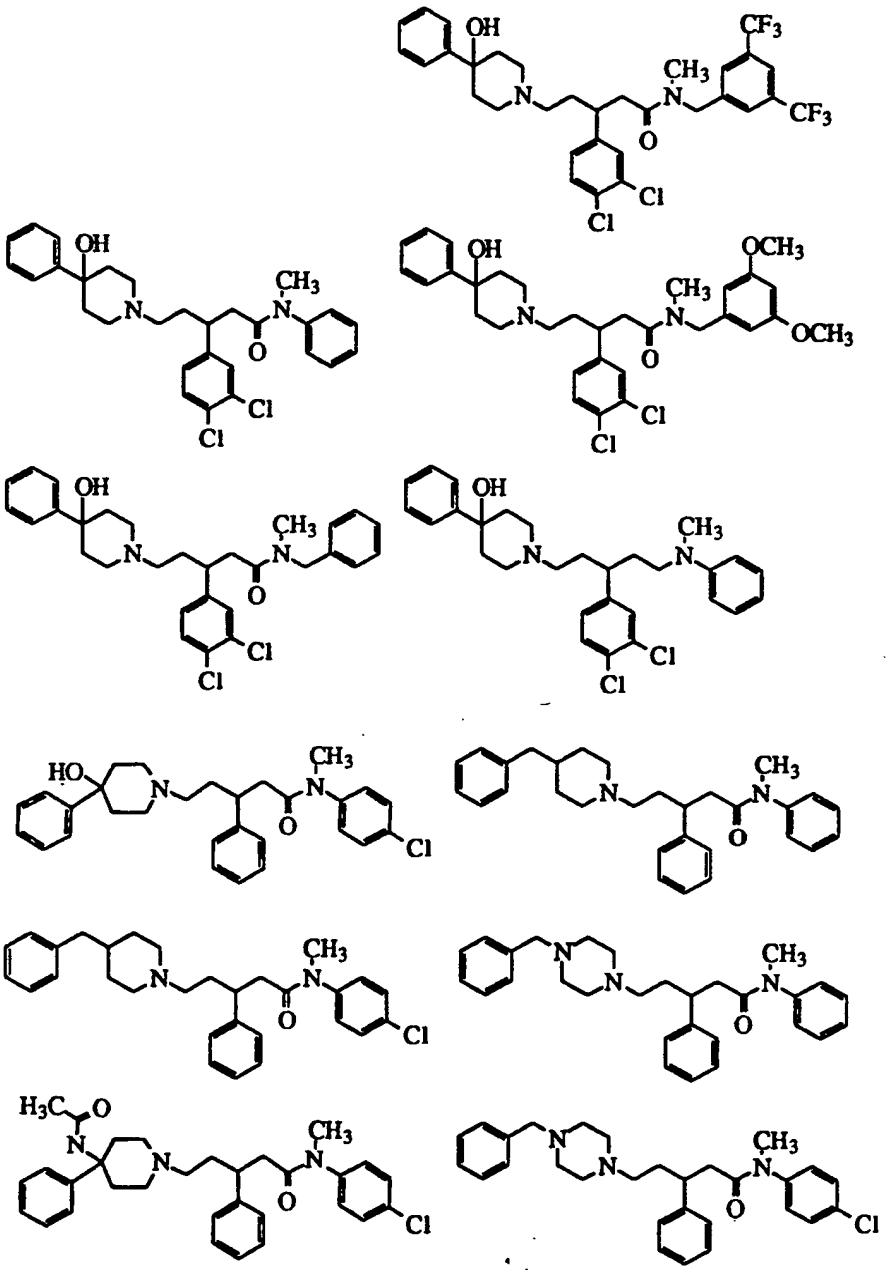
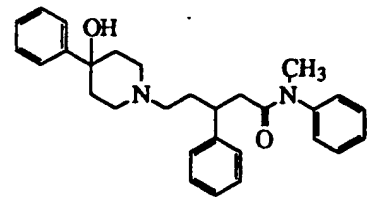


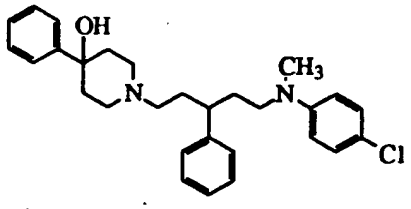
(D)

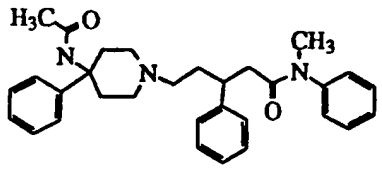
Exemplary compounds of the invention are the following, as well as pharmaceutically acceptable salts thereof:

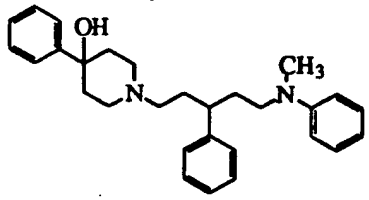


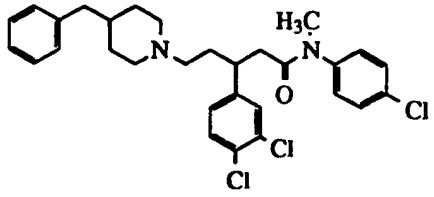


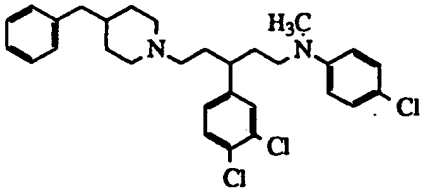


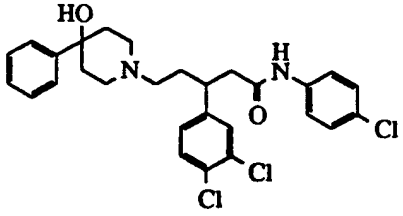


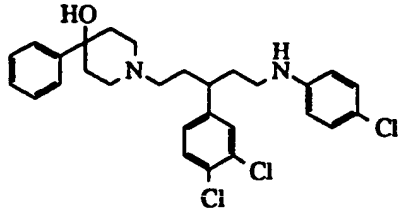


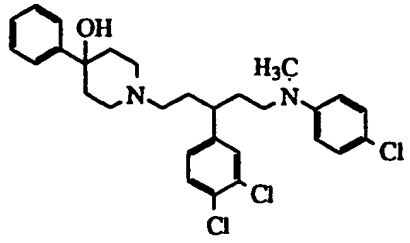


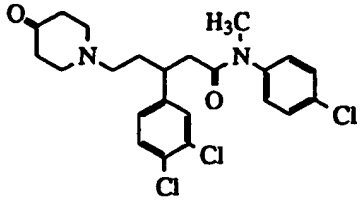












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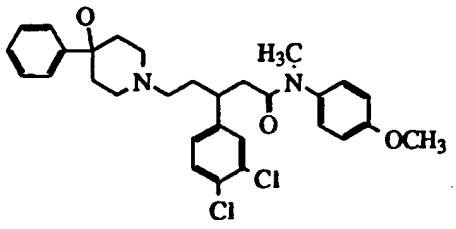
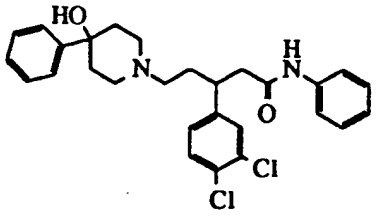
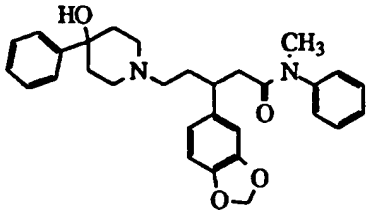
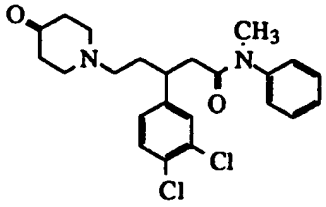
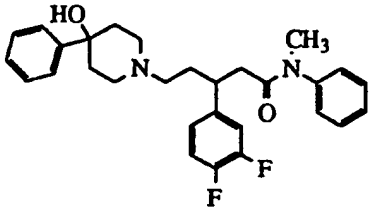
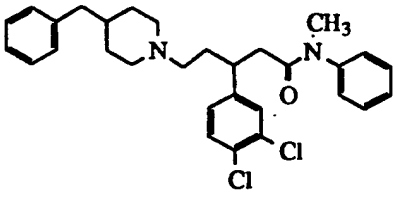


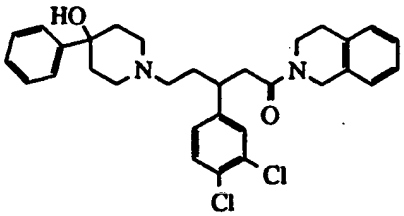


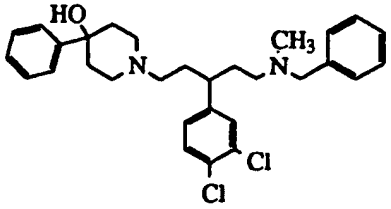


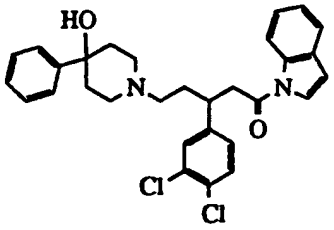


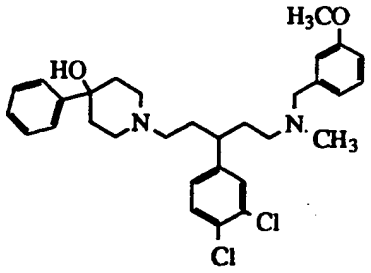












The invention also relates to a composition comprising a neurokinin antagonistic effective amount of a compound according to formula I and a pharmaceutically acceptable carrier material. The invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The invention also relates to a method for inducing neurokinin antagonism which comprises administering a neurokinin antagonistic effective amount of a compound according to formula I to a mammal in need thereof. The invention also relates to a method for treating chronic airway diseases such as asthma and allergies; inflammatory diseases such as inflammatory bowel disease, psoriasis, osteoarthritis, and rheumatoid arthritis; migraine; central nervous system disorders such as

depression, psychosis, dementia, and Alzheimer's disease; Down's syndrome; neuropathy; multiple sclerosis; ophthalmic disorders; conjunctivitis; auto immune disorders; graft rejection; systemic lupus erythematosus; GI disorders such as Crohn's disease and ulcerative colitis; disorders of bladder function; circulatory disorders such as angina; Raynaud's disease; coughing and pain. In particular, the invention also relates to a method of treating asthma which comprises administering to a mammal in need of such treatment an anti-asthma effective amount of a compound of formula I for such purpose.

Detailed Description of the Invention

As used herein the term alkyl means a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C_1-C_6 alkyl" represents a straight or branched, saturated hydrocarbon having from 1 to 6 carbon atoms.

The term alkenyl means a straight or branched, saturated alkenyl having from 2 to 6 carbon atoms. The number of carbon atoms may be designated. For example, "C_2-C_6 alkenyl" represents a straight or branched alkenyl having from 1 to 6 carbon atoms.

Asymmetric centers exist in compounds of formula I of the invention. Accordingly, compounds of formula I include stereoisomers. All such isomeric forms and mixtures thereof are within the scope of the present invention. Unless otherwise indicated, the methods of preparation disclosed herein may result in product distributions which include all possible structural isomers, although it is understood that physiological response may vary according to stereochemical structure. The isomers may be separated by conventional means such as fractional crystallization, preparative plate or column chromatography on silica, alumina, or reversed phase supports or HPLC (high performance liquid chromatography).

Enantiomers may be separated, where appropriate, by derivatization or salt formation with an optically pure reagent, followed

by separation by one of the aforementioned methods. Alternatively, enantiomers may be separated by chromatography on a chiral support.

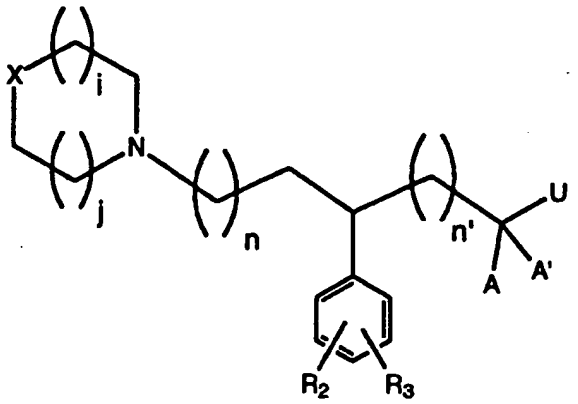
The compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g. the hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like are equivalent to the unsolvated forms for the purposes of the invention.

Those compounds of formula I which contain a basic group such as $-CH_2NH_2$, form pharmaceutically acceptable salts. The preferred pharmaceutically acceptable salts are nontoxic acid addition salts formed by adding to a suitable compound of the invention about a stoichiometric amount of a mineral acid , such as HCl, HBr, H_2SO_4 or H_3PO_4 or of an organic acid such as acetic, propionic, valeric, oleic, palmitic, stearic, lauric, benzoic, lactic, para-toluenesulfonic, methane sulfonic, citric, maleic, fumaric, succinic and the like, respectively.

General Methods of Preparation

The compounds of this invention may be prepared by one of the following general methods. Unless otherwise indicated, variables in the structural formulas below are as defined above.

The compounds of the present invention may be prepared from an appropriately substituted benzaldehyde as shown in Scheme 1 or from an appropriately substituted phenylacetic acid as shown in Scheme 2.

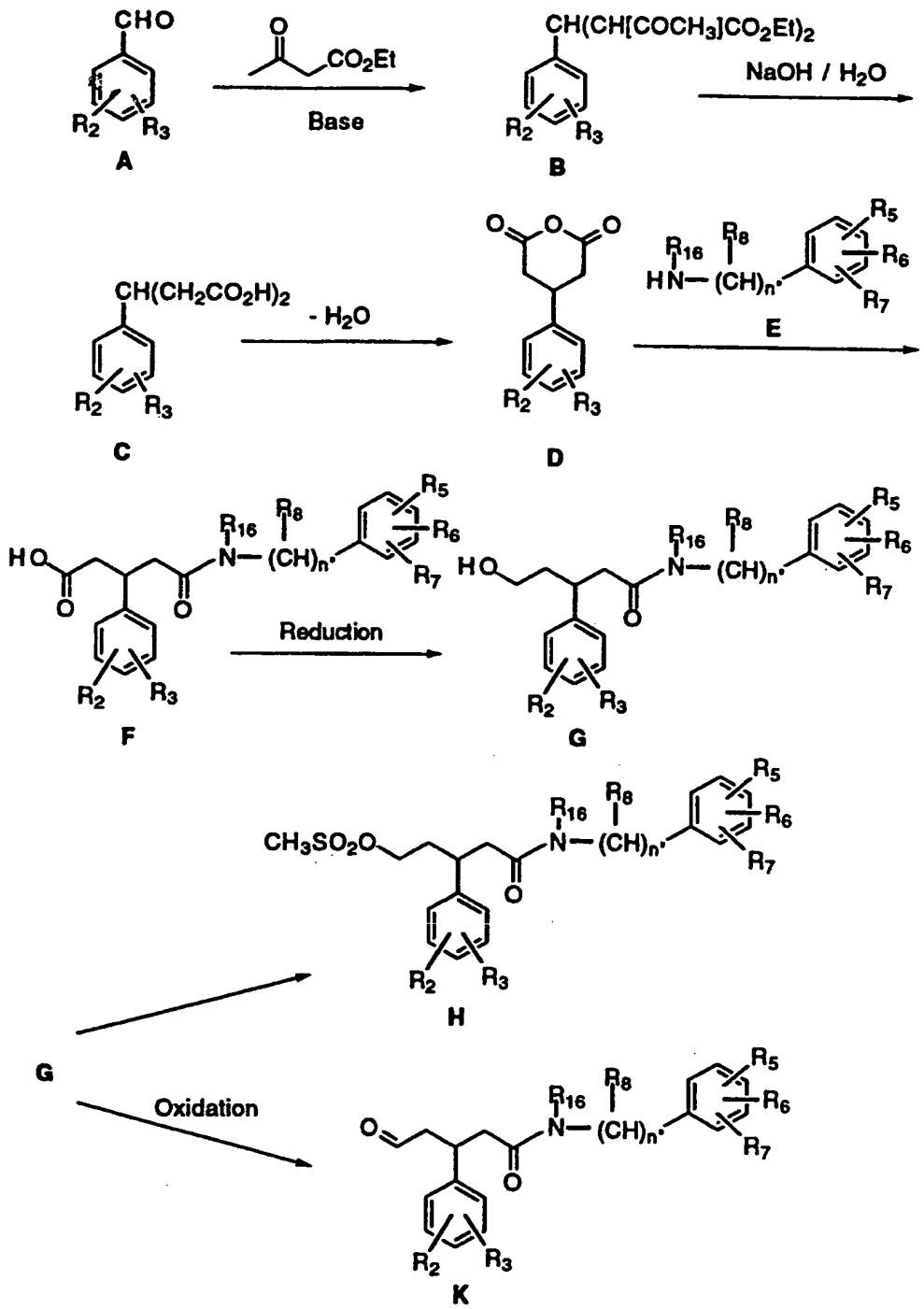


I

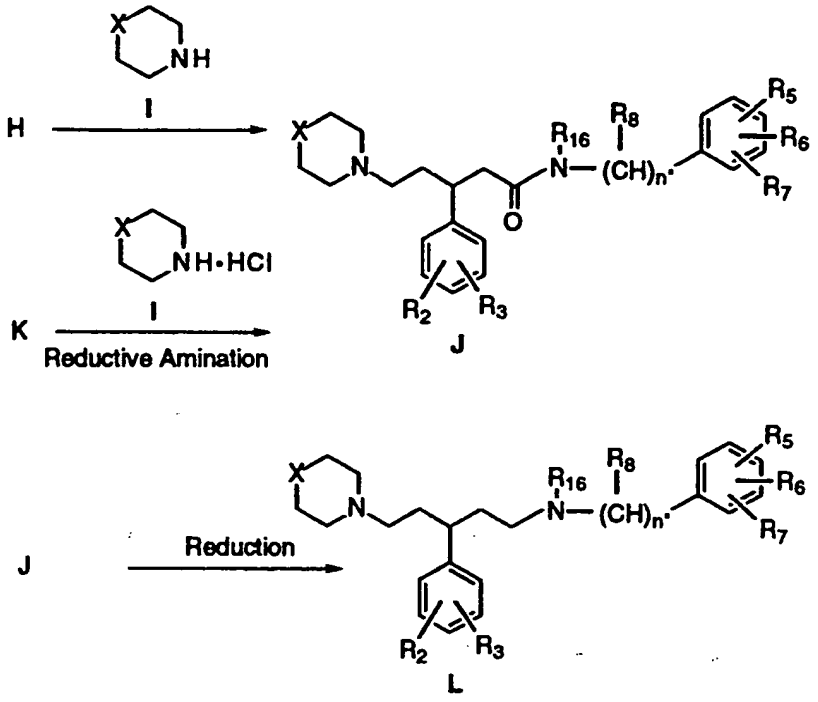
Methods for preparing th compounds of the present invention are illustrated in the following Schemes and examples. The compounds of the present invention may be prepared from an appropriately substituted benzaldehyde as shown in Scheme 1 or from an appropriately substituted phenylacetic acid as shown in Scheme 2.

Thus, as shown in Scheme 1, a benzaldehyde **A** is condensed with ethylacetoacetate in the presence of a base, for example an amine base such as piperidine, in a suitable solvent, for example an alcohol such as ethanol, as described in *J. Indian Chem. Soc.*, 1976, **53**, 1122, to give a bisacetoacetate **B**. Hydrolysis of **B** under strongly basic conditions using sodium hydroxide in an aqueous alcoholic solvent gives diacid **C**. Dehydration of **C** using an appropriate dehydrating agent, for example dicyclohexylcarbodiimide or acetyl chloride, then gives the substituted glutaric anhydride **D**. Treatment of anhydride **D** with an aniline or an arylalkylamine **E** in a suitable solvent, for example a halogenated solvent such as dichloromethane, in the presence of a suitable base, for example triethylamine or N,N-dimethylaminopyridine (DMAP), gives acid **F**. Reduction of the carboxylic acid function of **F** using a suitable reduction procedure, for example via the corresponding imidazolide or carbonic mixed anhydride and treatment with aqueous sodium borohydride, gives alcohol **G**. The alcohol **G** may then be converted to its corresponding halide or sulfonate **H**, for example by treatment with a sulfonyl halide in the presence of a base such as pyridine. Intermediate **H** may then be condensed with heterocyclic amine **I** in a suitable solvent, for example N,N-dimethylformamide, in the presence of a base, for example potassium carbonate or N,N-diisopropylethylamine, if desired to give **J**. In an alternative embodiment alcohol **G** may be oxidized, for example by the Swern procedure as described in *Tetrahedron*, 1978, **34**, 1651,to give aldehyde **K**. Aldehyde **K** may then be condensed with heterocyclic amine **I** in a reductive amination reaction, for example using sodium cyanoborohydride in methanol in the presence of a dehydrating agent such as molecular sieves, similar to that described in *J. Amer. Chem. Soc.*, 1971, **93**, 2897, to give **J**. The amide functionality of **J** may be

reduced, for example using borane-dimethylsulfide in tetrahydrofuran, to give amine **L**.

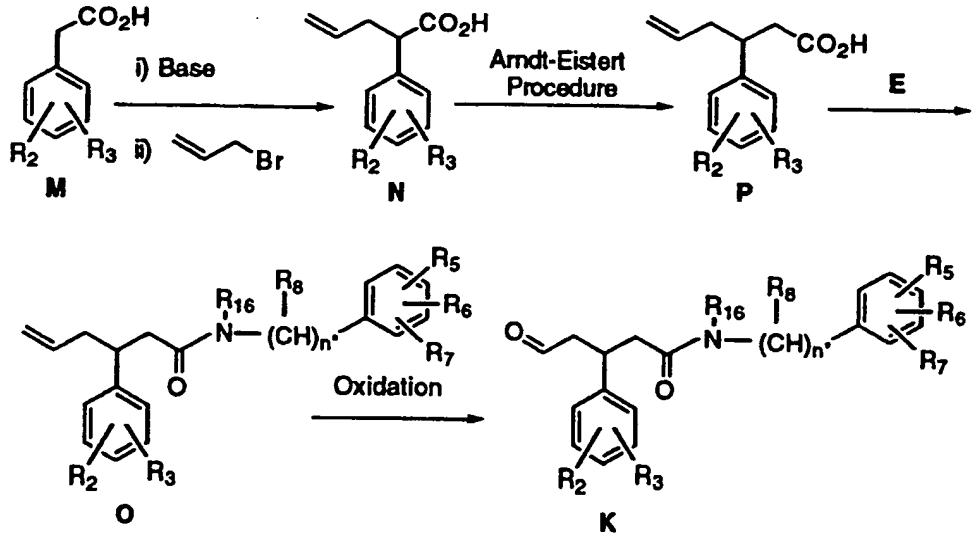


Scheme 1



Scheme 1 (contd.)

In an alternative synthesis, Scheme 2, a phenylacetic acid **M** may be converted to allyl acid **N**, for example as described in *Bioorganic Med. Chem. Letts.*, 1993, **3**, 319. Acid **N** may be homologated to acid **P** according to the Arndt-Eistert procedure, for example as described in *Chem. Pharm. Bull.*, 1981, **29**, 3249, and acid **P** may be condensed with an aniline or arylalkylamine **E** to give **O** (*n* = 1). Condensation of acid **P** may be accomplished via the corresponding acid chloride, prepared from **P** by treatment with oxalyl chloride and catalytic N,N-dimethylformamide, which may be used when **E** is an aniline or an arylalkylamine and is the preferred method when **E** represents an aniline. In an alternative procedure, when **E** is an arylalkylamine, condensation with **P** may be effected via the use of a carbodiimide, for example by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in dichloromethane. The allyl group of **O** can be oxidatively cleaved, for example upon treatment with ozone in methanol, to give aldehyde **K**. Aldehyde **K** may then be used in reductive amination reactions with heterocyclic amines **I** to give compound **J** as illustrated in Scheme 1.



Scheme 2.

The invention disclosed herein is exemplified by the following examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention will be apparent to those skilled in the art.

Example 1

β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinepentamide

Step A Diethyl-3,4-dichlorobenzal-*bis*-acetoacetate

3,4-Dichlorobenzaldehyde (100 g) in 95% ethanol (120 mL)was treated with ethylacetoacetate (146 mL) and stirred until a homogenous solution was obtained. This solution was treated with piperidine (8 mL) and left to stand for 18 hours. The crude product was recrystallized from 95% ethanol to give the title compound (230 g).

Step B 3-(3,4-Dichlorophenyl)glutaric acid

Diethyl-3,4-dichlorobenzal-*bis*-acetoacetate (155 g) in ethanol 2 L) was treated with 50% NaOH (2 L) and heated at reflux temperature for 4 hours. Water (1 L) was added to the reaction mixture and approx. 1.5 L of solvent removed by distillation. The remaining solution was poured

onto ice (1 Kg) and sufficient HCl was added to adjust the pH to 1. The resulting solution was extracted with EtOAc (3 X 1.5 L) and the combined extracts dried over $MgSO_4$, filtered and concentrated to give 100 g of the title compound.

Step C 3-(3,4-Dichlorophenyl)glutaric anhydride
3-(3,4-Dichlorophenyl)glutaric acid (100 g) was treated with acetyl chloride (300 mL) and the resulting mixture heated at reflux for 5 hours. The cooled reaction mixture was then azeotroped with toluene and concentrated under reduced pressure. The residue was slurried with diethyl ether (250 mL) and filtered to afford the title compound (86 g).

Step D 3,4-Dichloro-β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride in CH_2Cl_2 (20 mL) at 0°C was treated sequentially with N-methylaniline (0.518 g), triethylamine (0.489 g) and DMAP (trace). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (2X20 mL) and water (20 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (1.2 g).

Step E 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide
3,4-Dichloro-β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (0.98 g) in EtOAc (25 mL) was treated with CDI (0.653 g) and DMAP (trace). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (0.668 g) in H_2O (10 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et_2O and washed with 1N HCl (20 mL) , sat. $NaHCO_3$ (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressur to yield the title compound (0.908 g). Mass spectrum (CI): 352.

Step F 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide

3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide (0.9 g) in CH_2Cl_2 (25 mL) was cooled to -5 to -10°C and treated sequentially with Et_3N (0.332 g), and methanesulfonyl chloride (0.365 g). After two hours the reaction mixture was washed with water(3X20 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (1.1 g).

Step G β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidine pentamide

3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (1.1 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.14 g) and the mixture heated at 60°C for 18 hours. The cooled reaction mixture was diluted with EtOAc (100 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X100 mL) and the combined organic extracts, washed with water (100 mL) , dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH_2Cl_2:MeOH) gave the title compound (0.4 g). M.p. 67-72°, Mass spectrum (FAB): 513 (70%), 511 (100%).

Step H 3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide

Oxalyl chloride (7.74 g) in CH_2Cl_2 (80 mL) was added to a -78°C solution of DMSO (9.5 g) in CH_2Cl_2 (30 mL) over 15 mins. This mixture was stirred for 15 minutes whereupon a CH_2Cl_2 (50 mL) solution of 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide (17.15 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with a solution of Et_3N (14.76 g) in CH_2Cl_2 (20 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was washed with water (100 mL), the organic fraction separated, dried over $MgSO_4$,

filtered and concentrated under reduced pressure to yield an oil (20 g). Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (15.2 g).

Step I β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidine pentamide
3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (0.43 g), in MeOH (20 mL) was treated sequentially with molecular sieves 3A (2.0 g), 4-phenyl-4-hydroxypiperidine HCl (0.34 g) and $NaBH_3CN$ (0.32 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered through a pad of celite (trademark) and concentrated under reduced pressure. The residue was partitioned between 10% NH_4OH solution and CH_2Cl_2 (25 mL) The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2X25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude oil (0.7 g). Silica gel chromatography eluting with 1-2% $MeOH/CH_2Cl_2$ gave the title compound (0.42 g). Mass spectrum (CI): 524.

Example 2
1-[3-(3,4-Dichlorophenyl)-5-[(methyl)phenylamino]pentyl]-4-phenyl-4-piperidinol.

β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidine pentamide (0.22 g) in THF (25 mL) was treated with BH_3:DMS (0.212 mL; 10 M) and heated at reflux temperature for 18 hours. The cooled reaction mixture was then treated with MeOH (2.0 mL) and the solvent evaporated under reduced pressure. The residue was dissolved in EtOH (20 mL), treated with potassium carbonate (##.# g) and heated at reflux temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic portion was separated and the aqueous re-extracted with CH_2Cl_2 (2X20 mL). The combined

organic was dried over $MgSO_4$, filtered and vaporated to give the title compound (0.20 g). Mass spectrum (FAB): 515.

Example 3

β-(1,3-benzodioxol-5-yl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinepentamide

Step A Diethyl-(1,3-benzodioxol-5-yl)-*bis*-acetoacetate

Piperonal (25 g) in 95% ethanol (30 mL) was treated with ethylacetoacetate (42.5 mL) and stirred until a homogenous solution was obtained. Piperidine (2.3 mL) was added and the resulting solution stirred 18 hours. The crude product was obtained by filtration and subsequently recrystallized from 95% ethanol to give the title compound (35 g).

Step B 3-(1,3-Benzodioxol-5-yl)glutaric acid

Diethyl-3,4-methylenedioxybenzal-*bis*-acetoacetate (30 g) in ethanol (300 mL) was treated with 50% NaOH (300 mL) and heated at reflux for 4 hours. Approximately 250 mL of solvent removed by distillation. The remaining solution was cooled to 0°C and sufficient HCl was added dropwise to adjust the pH to 1. The resulting solution was extracted with EtOAc (3 x 500 mL) and the combined extracts dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a white solid (19 g).

Step C 3-(1,3-Benzodioxol-5-yl)glutaric anhydride

3-(1,3-benzodioxol-5-yl)glutaric acid (3.2 g) was treated with acetyl chloride (15 mL) and the resulting mixture heated at reflux for 5 hours. The cooled reaction mixture was then azeotroped with toluene (2 x 100 mL) and concentrated under reduced pressure. The residue was slurried with diethyl ether and filtered to afford the title compound (2.91 g).

Step D β-[2-[(phenyl)methylamino]-2-oxoethyl]-1,3-benzodioxol-5-ylpropanoic acid

3-(1,3-Benzodioxol-5-yl)glutaric anhydride (2.91 g) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with N-methylaniline (1.68 mL), triethylamine (2.16 mL) and DMAP (150 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1N HCl (1 x 150 mL) and water (1 x 150 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (4.2 g).

Step E β(2-hydroxyethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide

β-[2-[(phenyl)methylamino]-2-oxoethyl]-1,3-benzodioxol-5-yl-propanoic acid (4.2 g) in EtOAc (100 mL) was treated with CDI (2.51 g) and DMAP (146 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (2.34 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with 1N HCl (1 x 150 mL), sat. $NaHCO_3$ (1 x 150 mL) and water (1 x 150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (2.36 g). Mass spectrum (CI): 328.

Step F β(2-oxoethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide

A solution of β-(2-hydroxyethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide (500 mg) in CH_2Cl_2 (10 mL) was treated with PDC (570 mg) and molecular sieves (4Å, 570 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (374 mg).

Step G β-(1,3-benzodioxol-5-yl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinepentamide

β-(2-oxoethyl)-N-methyl-N-phenyl-1,3-benzodioxol-5-yl-propanamide (370 mg), in MeOH/THF (1:1, 10 mL) was treated sequentially with molecular sieves 3A (480 mg), 4-phenyl-4-hydroxypiperidine HCl (480 mg) and $NaBH_3CN$ (72 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (10mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (310 mg). Mass spectrum (CI): 487.

Example 4

β-(3,4-Difluorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinepentamide

Step A Diethyl-3,4-difluorobenzal-*bis*-acetoacetate

3,4-Difluorobenzaldehyde (5 g) in 95% ethanol (20 mL) was treated with ethylacetoacetate (18 mL) and stirred until a homogenous solution was obtained. Piperidine (1 mL) was added and the resulting solution stirred 18 hours. The crude product was obtained by filtration and subsequently recrystallized from 95% ethanol to give the title compound (11 g).

Step B 3-(3,4-Difluorophenyl)glutaric acid

Diethyl-3,4-difluorobenzal-*bis*-acetoacetate (11 g) in ethanol (150 mL) was treated with 50% NaOH (150 mL) and heated at reflux for 4 hours. Approximately 100 mL of solvent was removed by distillation. The remaining solution was cooled to 0°C and sufficient HCl was added dropwise to adjust the pH to 1. The resulting solution was extracted with EtOAc (3 x 300 mL) and the combined extracts dried over $MgSO_4$,

filtered and concentrated under reduced pressure to give the title compound as a white solid (7.4 g).

Step C 3-(3,4-Difluorophenyl)glutaric anhydride

3-(3,4-Difluorophenyl)glutaric acid (7.4 g) was treated with acetyl chloride (50 mL) and the resulting mixture heated at reflux for 5 hours. The cooled reaction mixture was then azeotroped with toluene (3 x 100 mL) and concentrated under reduced pressure. The residue was slurried with diethyl ether and filtered to afford the title compound (6.5 g).

Step D 3,4-Difluoro-β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Difluorophenyl)glutaric anhydride (3.61 g) in CH_2Cl_2 (75 mL) at 0°C was treated sequentially with N-methylaniline (2.16 mL), triethylamine (2.78 mL) and DMAP (195 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1N HCl (1 x 100 mL) and water (1 x 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (4.3 g).

Step E 3,4-Difluoro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide

3,4-Difluoro-β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (4.3 g) in EtOAc (100 mL) was treated with CDI (3.24 g) and DMAP (195 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (3.02 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with 1N HCl (1 x 100 mL), sat. $NaHCO_3$ (1 x 100 mL) and water (1 x 100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (3.64 g). Mass spectrum (CI): 320.

Step F 3,4-Difluoro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropamide

Oxalyl chloride (0.171 mL) in CH_2Cl_2 (10 mL) was added to a -78°C solution of DMSO (0.278 mL)in CH_2Cl_2 over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH_2Cl_2 solution of 3,4-difluoro-β-(2-hydroxyethyl)-N-methyl-N-phenylbenzene propanamide (500 mg) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with a solution of Et_3N (0.655 mL) in CH_2Cl_2 and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was washed with 0.1 N HCl (1 x 50 mL) and brine (1 x 50 mL. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (388 mg).

Step G β-(3,4-Difluorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinepentamide

3,4-Difluoro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropamide (520 mg), in MeOH/THF (1:1, 15 mL) was treated sequentially with molecular sieves 3A (700 mg), 4-phenyl-4-hydroxypiperidine HCl (700 mg) and $NaBH_3CN$ (103 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (570 mg). Mass spectrum (FAB): 479.2498.

Example 5

β-(3,4-Dichlorophenyl)-4-hydroxy-N,4-diphenyl -1-piperidinepentamide

Step A 3,4-Dichloro-β-[(2-phenylamino)-2-oxoethyl]-benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (5 g, Example 1, Step C) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with aniline (2.19 mL), triethylamine (3.3 mL) and DMAP (236 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1N HCl (1 x 150 mL) and water (1 x 150 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (5.4 g).

Step B 3,4-Dichloro-β-(2-hydroexyethyl)-N-phenylbenzenepropamide 3,4-Dichloro-β-[(2-phenylamino)-2-oxoethyl]-benzenepropanoic acid (4.5 g) in EtOAc (100 mL) was treated with CDI (2.6 g) and DMAP (156 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to -10°C and treated with a solution of $NaBH_4$ (2.42 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with 1N HCl (1 x 150 mL), sat. $NaHCO_3$ (1 x 150 mL) and water (1 x 150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (2 g). Mass spectrum (CI): 338.

Step C 3,4-Difluoro-β-(2-methanesulfonyloxyethyl)-N-phenylbenzenepropanamide
3,4-Dichloro-β-(2-hydroexyethyl)-N-phenylbenzenepropamide (340 mg) in CH_2Cl_2 was cooled to -5 to -10°C and treated sequentially with Et_3N (0.278 mL) and methanesulfonyl chloride (0.097 mL). After one hour the reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed with sat. NaHCO3 (1 x 50 mL) The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (480 mg).

Step D β-(3,4-Dichlorophenyl)-4-hydroxy-N,4-diphenyl -1-piperidinepentamide

3,4-Difluoro-β-(2-methan sulfonyloxyethyl)-N-phenylbenzenepropanamide (480 mg) in DMF (5 mL) was treated with 4-phenyl-4-hydroxypiperidine (177 mg) and the mixture stirred at room temperature for 18 hours. The reaction mixture was diluted the EtOAc (50 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc and the combined organic extracts, washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH_2Cl_2:MeOH) gave the title compound (246 mg). Mass spectrum (CI): 497.

Example 6

N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl)-4-hydroxy-4-phenyl -1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[(4-chlorophenyl)amino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride in CH_2Cl_2 (75 mL) at 0°C was treated sequentially with 4-chloroaniline (2.25 g), triethylamine (1.79 g) and DMAP (trace). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (3X50 mL) and water (50 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (4.9 g).

Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-(4-chlorophenyl)benzenepropanamide

3,4-Dichloro-β-[2-[(4-chlorophenyl)amino]-2-oxoethyl]benzene propanoic acid (4.0 g) in EtOAc (75 mL) was treated with CDI (2.52 g) and DMAP (trace). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (2.59 g) in H_2O (40 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et_2O and washed with 1N HCl (100 mL) , sat. $NaHCO_3$ (100 mL) and water (100

mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (3.81 g).

Step C 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-(4-chlorophenyl)benzenepropanamide

3,4-Dichloro-β-(2-hydroxyethyl)-N-(4-chlorophenyl)benzene propanamide (3.5 g) in CH_2Cl_2 (60 mL) was cooled to -5 to -10°C and treated sequentially with Et_3N (1.19 g), and methanesulfonyl chloride (1.35 g). After two hours the reaction mixture was washed with water(3X50 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (3.8 g).

Step D N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl)-4-hydroxy-4-phenyl -1-piperidine-pentamide

3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-phenylbenzenepropanamide (3.8 g) in DMF (50 mL) was treated with 4-phenyl-4-hydroxypiperidine (3.74 g) and the mixture heated at 60°C for 18 hours. The cooled reaction mixture was diluted the EtOAc (100 mL) and water (100 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X100 mL) and the combined organic extracts, washed with water (100 mL) , dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 5% MeOH:CH_2Cl_2 gave the title compound (1.2 g). Mass spectrum (FAB): 386.

Example 7

1-[5-(4-Chlorophenyl)amino]-3-(3,4-dichlorophenyl)pentyl]-4-phenyl-4-piperidinol.

The title compound was prepared from N-(4-Chlorophenyl)-β-(3,4-dichlorophenyl)-4-hydroxy-4-phenyl -1-piperidine-pentamide following the procedure of Example 2. Mass spectrum (FAB): 517.

Example 8

4-Hydroxy-N-methyl-N, β,4-triphenyl-1-piperidinepentanamide

Step A 3-Phenylglutaric anhydride

3-Phenylglutaric acid (100 g) in CH_2Cl_2 (800 mL) was treated with dicyclohexylcarbodiimide (104 g) in CH_2Cl_2 (400 mL) over 30 minutes. The resulting mixture was stirred at ambient temperature for 48 hours. The reaction mixture was then diluted with hexane (800 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue crystallized from ethyl acetate/hexane to afford the title compound (53 g).

Step B β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-Phenylglutaric anhydride (8.0 g) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with N-methylaniline (5.63 g), triethylamine (5.32 g) and DMAP (1.0 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (2X50 mL) and water (100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (11.5 g).

Step C β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide

β-[2-[(phenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (11.5 g) in EtOAc (225 mL) was treated with CDI (11.68 g) and DMAP (1.0 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (9.74 g) in H_2O (150 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et_2O and washed with 1N HCl (100 mL) , sat. $NaHCO_3$ (100 mL) and water (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (10.4 g).

Step D β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide

β-(2-hydroxyethyl)-N-methyl-N-phenylbenzenepropanamide (5.0 g) in CH_2Cl_2 (100 mL) was cooled to -5 to -10°C and treated sequentially

with Et_3N (2.23 g), and methanesulfonyl chloride (2.53 g). After two hours the reaction mixture was washed with water(3X50 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (6.4 g).

Step E 4-Hydroxy-N-methyl-N, β,4-triphenyl-1-piperidinepentanamide β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (2.0 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.44 g) and the mixture heated at 60°C for 18 hours. The cooled reaction mixture was diluted the EtOAc (100 mL) and water (100 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X100 mL) and the combined organic extracts, washed with water (100 mL) , dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography gave the title compound (0.8 g). Mass spectrum (FAB): 443.

Example 9

1-[5-[(Phenyl)methylamino]-3-phenylpentyl]-4-phenyl-4-piperidinol.

The title compound was prepared from 4-Hydroxy-N-methyl-N, β,4-triphenyl-1-piperidinepentanamide following the procedure of Example 2. Mass spectrum (CI): 429.

Example 10

N-(4-Chlorophenyl)-4-hydroxy-N-methyl-β,4-diphenyl-1-piperidinepentanamide

Step A β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-Phenylglutaric anhydride (2.0 g) in CH_2Cl_2 (25 mL) at 0°C was treated sequentially with 4-chloro-N-methylaniline (1.86 g), triethylamine (1.33 g) and DMAP (trace). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (2X50 mL) and water (100

mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (2.7 g).

Step B N-(4-Chlorophenyl)-β-(2-hydroxyethyl)-N-methyl-benzenepropanamide

β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (1.3 g) in EtOAc (25 mL) was treated with CDI (0.957 g) and DMAP (trace). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (0.983 g) in H_2O (15 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et_2O and washed with 1N HCl (20 mL) , sat. $NaHCO_3$ (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (1.25 g).

Step C N-(4-Chlorophenyl)-β-(2-methanesulfonyloxyethyl)-N-methyl-benzenepropanamide

N-(4-Chlorophenyl)-β-(2-hydroxyethyl)-N-methyl-benzene propanamide (1.25 g) in CH_2Cl_2 (25 mL) was cooled to -5 to -10°C and treated sequentially with Et_3N (0.497 g), and methanesulfonyl chloride (0.563 g). After two hours the reaction mixture was washed with water(3X25 mL), sat. $NaHCO_3$ (20 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (1.44 g).

Step D N-(4-Chlorophenyl)-4-hydroxy-N-methyl-β,4-diphenyl-1-piperidinepentanamide

N-(4-Chlorophenyl)-β-(2- methanesulfonyloxyethyl)-N-methyl-benzenepropanamide (1.44 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.61 g) and the mixture heated at 80°C for 2 hours. The cooled reaction mixture was diluted the EtOAc (50 mL) and water (50 mL) and the aqueous phase removed. The aqueous layer was extracted with EtOAc (2X50 mL) and the combined organic extracts, washed with water (50 mL) , dried over $MgSO_4$, filtered and

concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 10% MeOH:CH_2Cl_2 gave the title compound (0.7 g). Mass spectrum (FAB): 477.

Example 11

1-[5-[(4-Chlorophenyl)methylamino]-3-phenylpentyl]-4-phenyl-4-piperidinol.

The title compound was prepared from N-(4-Chlorophenyl)-4-hydroxy-N-methyl-β,4-diphenyl-1-piperidinepentanamide following the procedure of Example 2. Mass spectrum (FAB): 463.3.

Example 12

4-(Acetylamino)-N-methyl-N, β,4-triphenyl-1-piperidinepentanamide

The title compound was prepared from β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide, (which comes from Example 8, step D), using 4-acetylamino-4-phenylpiperidine hydrochloride in a procedure analogous to that of Example 8, Step E. Mass spectrum (FAB): 484.4.

Example 13

4-(Acetylamino)-N-(4-chlorophenyl)-N-methyl-β,4-diphenyl-1-piperidinepentanamide

The title compound was prepared from N-(4-Chlorophenyl)-β- (2-methanesulfonyloxyethyl)-N- methyl- benzenepropanamide (which comes from Example 10, Step C), using 4-acetylamino-4-phenylpiperidine hydrochloride in a procedure similar to that of Example 10, Step D. Mass spectrum (FAB): 518.3.

Example 14

N-Methyl-N, β-diphenyl-4-(phenylmethyl)-1-piperidinepentanamide

The title compound was prepared from β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 8, step D), using a procedure similar to that of Example 8, step E. Mass spectrum (FAB): 441.1.

Example 15

N-(4-Chlorophenyl)-N-methyl-*b*-phenyl-4-(phenylmethyl)-1-piperidinepentamide

The title compound was prepared from N-(4-Chlorophenyl)-β- (2-methanesulfonyloxyethyl)-N- methyl- benzenepropanamide (which comes from Example 10, step C), using 4-benzylpiperidine in a procedure similar to that of Example 10, step D. Mass spectrum (FAB): 475.2.

Example 16

N-Methyl-N, β-diphenyl-4-(phenylmethyl)-1-piperazinepentanamide

The title compound was prepared from β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 8, step D), using N-phenylmethylpiperizine in a procedure similar to that of Example 8, Step E. Mass spectrum (FAB): 442.1.

Example 17

N-(4-Chlorophenyl)-N-methyl-β -phenyl-4-(phenylmethyl)-1-piperazinepentanamide

The title compound was prepared from N-(4-Chlorophenyl)-β-(2-methanesulfonyloxyethyl)-N-methyl-benzenepropanamide (which comes from Example 10, step C), using N-phenylmethylpiperazine in a procedure similar to that of Example 10, step D. Mass spectrum (FAB): 476.3.

Example 18

β-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-N-phenyl-2-isoquinolinepentamide

3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 1, step H) (0.53 g), in MeOH (35 mL) was treated sequentially with molecular sieves 3A (5.5 g), isoquinoline HCl (0.33 g) and $NaBH_3CN$ (0.4 g). The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered through a pad of celite (trademark) and concentrated under reduced pressure. The residue was partitioned between 10% NH_4OH solution and CH_2Cl_2 (25 mL) The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2X25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude oil (0.7 g). Silica gel chromatography eluting with 2% MeOH/CH_2Cl_2 gave the title compound (0.27 g). Mass spectrum (FAB): 467.

Example 19

3-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-N-phenyl-2-isoquinolinepentanamine

The title compound was prepared from β-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-N-phenyl-2-isoquinolinepentamide following the procedure of Example 2. Mass spectrum (FAB): 453.

Example 20

β-(3,4-Dichlorophenyl)-3,4-dihydro-6-methoxy-N-methyl-4-oxo-N-phenyl-spiro[2H-1-benzopyran-2,4'-piperidine]-1'-pentamide

The title compound was prepared from 3,4-dichloro-β-(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 1, Step H) using 3,4-dihydro-6-methoxy-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidine] HCl in a procedure similar to that of Example 18. Mass spectrum (FAB): 581.

Example 21

1'-[3-(3,4-Dichlorophenyl)-5-(methylphenylamino)pentyl]-3,4-dihydro-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperid]-4-ol

The title compound was prepared from β -(3,4-Dichlorophenyl)-3,4-dihydro-6-methoxy-N-methyl-4-oxo-N-phenyl-spiro[2H-1-benzopyran-2,4',-piperidine]-1' pentamide following the procedure of Example 2. Mass spectrum (FAB): 569.

Example 22

β -(3,4-Dichlorophenyl)-N-methyl-4-oxo-N-phenyl-1-piperidinepentamide

The title compound was prepared from 3,4-Dichloro-β –(2-oxoethyl)-N-methyl-N-phenylbenzenepropamide (which comes from Example 1 Step H), Mass spectrum (FAB): 433.1457.

Example 23

β -(3,4-Dichlorophenyl)-N-methyl-N-phenyl-4-(phenylmethyl)-1-piperidinepentamide

The title compound was prepared from 3,4-dichloro-β -(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (which comes from Example 1 Step H), using a procedure similar to that of Example 18. Mass spectrum (FAB): 509.

Example 24

N-(4-Chlorophenyl)-β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl -1-piperidinepentanamide

Step A 3,4-Dichloro-β -[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (10.0 g) in CH_2Cl_2 (150 mL) at 0°C was treated sequentially with 4-chloro-N-methylaniline (6.8 g), triethylamine (4.87 g) and DMAP (0.5 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (3X100 mL)

and water (100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (14.9 g).

Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-(4-chlorophenyl)-N-methylbenzenepropanamide

3,4-Dichloro-β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (14.9 g) in EtOAc (270 mL) was treated with CDI (9.1 g) and DMAP (trace). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (9.32 g) in H_2O (140 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with Et_2O and washed with 1N HCl (3X100 mL) , sat. $NaHCO_3$ (250 mL) and water (250 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (12.64 g).

Step C 3,4-Dichloro-β -(2-methanesulfonyloxyethyl)-N-(4-chlorophenyl)-N-methylbenzenepropanamide

3,4-Dichloro-β -(2-hydroxyethyl)-N-(4-chlorophenyl)-N-methylbenzenepropanamide (2.1 g) in CH_2Cl_2 (40 mL) was cooled to -5 to -10°C and treated sequentially with Et_3N (0.69 g), and methanesulfonyl chloride (0.78 g). After two hours the reaction mixture was washed with water(3X50 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (2.3 g).

Step D N-(4-Chlorophenyl)-β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentanamide

3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-phenylbenzenepropanamide (1.6 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (0.61 g) and K_2CO_3 (0.476 g). The mixture was stirred at ambient temperature then diluted with EtOAc (100 mL) and washed with H_2O (2X100 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give

an oil. Silica gel chromatography eluting with 95:5 (CH_2Cl_2:MeOH) gave the title compound (0.56 g). Mass spectrum (FAB): 545.3.

Example 25

1-[5-(4-Chlorophenyl)(methyl)amino]-3-[3,4-dichlorophenyl]-pentyl]-4-phenyl-4-piperidinol.

The title compound was prepared from N-(4-chlorophenyl)-β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl -1-piperidinepentanamide following the procedure of Example 2. Mass spectrum (FAB): 531.1.

Example 26

N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl)-N-methyl-4-oxo-1-piperidinepentanamide

Step A 3,4-Dichloro-β-(2-bromoethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide

3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide (6.3 g, from Example 27, Step C) in THF (50 mL) was treated with lithium carbonate (2.0 g) and lithium bromide (2.34 g). The mixture was heated at reflux temperature for 2 hours. The cooled reaction mixture was diluted the CH_2Cl_2 (100 mL) and washed with H_2O (2X100 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as a yellow oil, (5.6 g).

Step B N-(4-Chlorophenyl)-β -(3,4-Dichlorophenyl)-N-methyl-4-oxo-1-piperidine pentanamide

3,4-Dichloro-β-(2-bromoethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide (4.6 g) in DMF (60 mL) was treated with 4-piperidone monohydrate hydrochloride (3.94 g) and K_2CO_3 (5.3 g). The mixture was stirred vigorously at ambient temperature for 120 hours. The reaction mixture was poured into H_2O (100 mL) and xtracted with EtOAc (2X100 mL). The organic extracts were dried over $MgSO_4$,

filtered and concentrated under r duced pressur to give an oil. Silica gel chromatography eluting with 95:5 (CH_2Cl_2:MeOH) gave the title compound (2.25 g). Mass spectrum (FAB): 467.1.

Example 27
N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinepentanamide

Step A 3,4-Dichloro-β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (5.0 g) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with 4-chloro-N-methylaniline (2.92 mL)), triethylamine (3.36 mL) and DMAP (0.24 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (2X100 mL) and water (2X100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (6.63 g).

Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(4-chlorophenyl)-benzenepropanamide
3,4-Dichloro-β-[2-[(4-chlorophenyl)methylamino]-2-oxoethyl] benzenepropanoic acid (4.0 g) in EtOAc (75 mL) was treated with CDI (2.43 g) and DMAP (0.122 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for one hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (2.45 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (100 mL) and washed with H_2O (100 mL), 1N HCl (100 mL) , and sat. $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (3.69 g).

Step C 3,4-Dichloro-β-(2-methanesulfonyloxyethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide

3,4-Dichloro-β-(2-hydroxyethyl)-N-m thyl-N-(4-chloroph nyl) -benzenepropanamide (3.6 g) in CH_2Cl_2 (100 mL) was cooled to -5 to -10°C and treated sequentially with Et_3N (1.62 mL), and methanesulfonyl chloride (0.9 mL). After two hours the reaction mixture was washed with water (100 mL), brine (100 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (4.3 g).

Step D N-(4-Chlorophenyl)-β-(3,4-Dichlorophenyl) -N-methyl-4-(phenylmethyl)-1-piperidinepentanamide
3,4-Dichloro-β-(2- methanesulfonyloxyethyl)-N-methyl-N-(4-chlorophenyl)benzene propanamide (1.6 g) in DMF (10 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.14 g) and K_2CO_3 (0.476 g). The mixture was heated at 60°C for 18 hours. The cooled reaction mixture was diluted the EtOAc (100 mL) and washed with H_2O (2X100 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 95:5 (CH_2Cl_2:MeOH) gave the title compound (0.56 g). M.p. 67-72°, Mass spectrum (CI): 543.

Example 28
N-(4-Chlorophenyl)-*gamma* -(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinepentanamine

The title compound was prepared from N-(4- Chlorophenyl)-β-(3,4-Dichlorophenyl)-N-methyl-4-(phenylmethyl)-1-piperidinepentanamide using the procedure of Example 2. Mass spectrum (CI): 529.

Example 29
β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N-(4-methoxyphenyl)-4-phenyl-1-piperidinepentanamide

Step A 3,4-Dichloro-β -[2-[(4-methoxyphenyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (5.0 g) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with 4-methoxy-N-methylaniline (3.3 g)), triethylamine (3.36 mL) and DMAP (0.24 g). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (100 mL) and water (2X100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (7.3 g).

Step B 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-(4-methoxyphenyl)-benzenepropanamide
3,4-Dichloro-β -[2-[(4-methoxyphenyl)methylamino]-2-oxoethyl]benzenepropanoic acid (7.2 g) in EtOAc (125 mL) was treated with CDI (4.4 g) and DMAP (0.22 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for one hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (4.46 g) in H_2O (75 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (100 mL) and washed with H_2O (100 mL), 1N HCl (100 mL) , and H_2O (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 60-100% EtOAc/hexane gave the title compound (5.43 g).

Step C 3,4-Dichloro-β -(2-methanesulfonyloxyethyl)-N-methyl-N-(4-methoxyphenyl)benzene propanamide
3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-(4-methoxyphenyl)-benzene propanamide (2.0 g) in CH_2Cl_2 (50 mL) was cooled to -5 to -10°C and treated sequentially with Et_3N (0.911 mL), and methanesulfonyl chloride (0.64 mL). After two hours the reaction mixture was washed with water (100 mL), brine (100 mL) and the organic layer separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (2.56 g).

Step D β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N-(4-methoxyphenyl)-4-phenyl-1-piperidinepentanamide

3,4-Dichloro-β-(2-methanesulfonyloxyethyl) -N-methyl-N-(4-methoxyphenyl)benzene propanamide (4.2 g) in DMF (20 mL) was treated with 4-phenyl-4-hydroxypiperidine (1.53g) and K_2CO_3 (1.19 g). The mixture was heated at 60°C for 18 hours. The cooled reaction mixture was diluted the EtOAc (200 mL) and washed with H_2O (3X150 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil. Silica gel chromatography eluting with 90:10 (CH_2Cl_2:MeOH) gave the title compound (0.58 g). Mass spectrum (CI): 541.

Example 30

N-[3,5-*bis*-(Trifluoromethyl)phenyl]-β-(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[(3,5-*bis*-trifluoromethylphenyl)amino)]-2-oxoethyl]-benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH_2Cl_2 (300 mL) at 0°C was treated sequentially with 3,5-*bis*-(trifluoromethyl)aniline (7.5 mL), triethylamine (6.7 mL) and DMAP (470 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (18 g).

Step B 3,4-Dichloro-β-[2-[(3,5-*bis*-trifluoromethylphenyl)methylamino)]-2-oxoethyl]-benzenepropanoic acid

Sodium hydride (2.16 g, 95%) was suspended in THF (100 mL) and cooled to 0°C. 3,4-Dichloro-β-[2-[(3,5-*bis*-trifluoromethylphenyl)methylamino)]-2-oxoethyl]-benzenepropanoic acid (18 g), in THF (100 mL) was added dropwise. After addition the mixture was warmed to room temperature and stirred for 12 hours. The mixture was then heated at reflux for 1 hour. The mixture was cooled to room temperature and methyl iodide (2.6 mL) was added dropwise. The resulting mixture was heated at reflux for 24 hours. Cooled to 0°C and

quenched carefully with H_2O (100 mL). Extracted with EtOAc (3 x 200 mL). The combine organic layers were dried over MgSO4, filtered and concentrated under reduced pressure to give crude product. Silica gel chromatography eluting with 0-50% MeOH/CH_2Cl_2 gave the title compound (8.5 g).

Step C N-(3,5-*bis*-trifluoromethylphenyl)-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzenepropanamide

3,4-Dichloro-β-[2-[(3,5-*bis*-trifluoromethylphenyl)methylamino)]-2-oxoethyl]-benzenepropanoic acid (7.8 g) in EtOAc (100 mL) was treated with CDI (3.16 g) and DMAP (190 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (2.95 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl (1 x 200 mL), sat. $NaHCO_3$ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (6 g). Mass spectrum (CI): 488.

Step D N-(3,5-*bis*-trifluoromethylphenyl)-3,4-dichloro-β-(2-oxoethyl)-N-methyl-benzenepropamide

A mixture of N-(3,5-*bis*-trifluoromethylphenyl)-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzenepropanamide (1.3 g) and molecular sieves (4A, 624 mg) in CH_2Cl_2 (20 mL) and was treated with TPAP (47 mg) and 4-methylmorpholine-N-oxide (624 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (810 mg).

Step E N-[3,5-*bis*-(Trifluoromethyl)phenyl]-β-(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

N-(3,5-*bis*-trifluoromethylphenyl)-3,4-dichloro-β -(2-oxoethyl)-N-methyl-benzenepropamide (810 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with molecular sieves 3A (534 mg), 4-phenyl-4-hydroxypiperidine HCl (534 mg) and $NaBH_3CN$ (104 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (700 mg). Mass spectrum (FAB): 647.1663.

Example 31

β -(3,4-dichlorophenyl)-4-hydroxy-N-(2-methoxyphenyl)-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[(2-methoxyphenyl)amino]-2-oxoethyl]-benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH_2Cl_2 (150 mL) at 0°C was treated sequentially with *o*-anisidine (6 mL), triethylamine (6.7 mL) and DMAP (440 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (14 g).

Step B 3,4-Dichloro-β-[2-[(2-methoxyphenyl)methylamino)]-2-oxoethyl]-benzenepropanoic acid

Sodium hydride (1.94 g, 95%) was suspended in THF (100 mL) and cooled to 0°C. 3,4-Dichloro-β-[2-[(2-methoxyphenyl)amino]-2-oxoethyl]-benzenepropanoic acid (14 g), in THF (150 mL) was added dropwise. After addition the mixture was warmed to room temperature and stirred for 12 hours. The mixture was then heated at reflux for 1 hour. The

mixture was cooled to room temperatur and methyl iodide (2.40 mL) was added dropwise. The resulting mixture was heated at reflux for 24 hours. Cooled to 0°C and quenched carefully with H_2O (100 mL). Extracted with EtOAc (3 x 200 mL). The combine organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude product. Silica gel chromatography eluting with 0-50% MeOH/CH_2Cl_2 gave the title compound (10 g).

Step C 3,4-dichloro-β-(2-hydroxyethyl)-N-(2-methoxyphenyl)-N-methylbenzenepropanamide

3,4-Dichloro-β-[2-[(2-methoxyphenyl)methylamino)]-2-oxoethyl]-benzenepropanoic acid (7.8 g) in EtOAc (100 mL) was treated with CDI (3.16 g) and DMAP (190 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (2.95 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl (1 x 200 mL), sat. $NaHCO_3$ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (8 g). Mass spectrum (CI): 382.

Step D 3,4-dichloro-β-N-(2-methoxyphenyl)-N-methyl-(2-oxoethyl)-benzenepropamide

A solution of oxalyl chloride (1.14 mL) in CH_2Cl_2 (50 mL) was cooled to -78°C whereupon DMSO (1.85 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH_2Cl_2 (10 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-(2-methoxyphenyl)-N-methylbenzenepropanamide (1.0 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et_3N (7.3 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH_2Cl_2 (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO3 (1 x 50 mL)

and brin (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (950 mg).

Step E β -(3,4-dichlorophenyl)-4-hydroxy-N-(2-methoxyphenyl)-N-methyl-4-phenyl-1-piperidinepentamide
3,4-dichloro-β -N-(2-methoxyphenyl)-N-methyl-(2-oxoethyl)-benzenepropamide (950 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with molecular sieves 3A (800 mg), 4-phenyl-4-hydroxypiperidine HCl (800 mg) and $NaBH_3CN$ (156 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (720 mg). Mass spectrum (CI): 541.

Example 32
1-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroquinoline

Step A β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-quinolinepentanoic acid.
3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH_2Cl_2 (300 mL) at 0°C was treated sequentially with 1,2,3,4-tetrahydroquinoline (5.6 mL), triethylamine (6.3 mL) and DMAP (472 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (14.3 g).

Step B 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroquinoline

β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-quinolinepentanoic acid (14.3 g) in EtOAc (300 mL) was treated with CDI (7.42 g) and DMAP (450 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (5.5 g) in H_2O (100 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (500 mL) and washed with 1N HCl (1 x 200 mL), sat. $NaHCO_3$ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (11.5 g). Mass spectrum (CI): 378.

Step C 1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroquinoline

A solution of oxalyl chloride (1.15 mL) in CH_2Cl_2 (30 mL) was cooled to -78°C whereupon DMSO (1.87 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH_2Cl_2 (30 mL) solution of 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroquinoline (1.0 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et_3N (7.4 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH_2Cl_2 (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO3 (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (900 mg).

Step E 1-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroquinoline

1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroquinoline (900 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with

molecular sieves 3A (767 mg), 4-phenyl-4-hydroxypiperidine HCl (767 mg) and $NaBH_3CN$ (150 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (750 mg). Mass spectrum (FAB): 537.2081.

Example 33

β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(phenylmethyl)-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[(phenylmethyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (5.0 g) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with N-methyl-N-(phenylmethyl)amine (3.0 mL), triethylamine (3.36 mL) and DMAP (0.26)). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was washed with 1N HCl (100 mL) and water (2X100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (6.9 g).

Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide

3,4-Dichloro-β-[2-[(phenylmethyl)methylamino]-2-oxoethyl]benzenepropanoic acid (6.9 g) in EtOAc (150 mL) was treated with CDI (4.4 g) and DMAP (0.22 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (4.46 g) in H_2O (75 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL) , H_2O (250 mL) and

dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (6.29 g).

Step C 3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide

Oxalyl chloride (1.11 mL) in CH_2Cl_2 (10 mL) was added to a -78°C solution of DMSO (1.8 mL) in CH_2Cl_2 (75 mL) over 15 minutes. This mixture was stirred for 15 minutes whereupon a CH_2Cl_2 (20 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-phenylmethyl)benzenepropanamide (3.72 g) was added dropwise. The mixture was stirred for 30 minutes and then treated with a solution of Et_3N (4.24 mL) in CH_2Cl_2 (10 mL) and stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature overnight. The reaction mixture was washed with water (100 mL), the organic fraction separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil (4.3 g). Silica gel chromatography eluting with 1:1/EtOAc:Hex gave the title compound (3.09 g).

Step D β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl -N-(phenylmethyl)-1-piperidine pentamide

3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-(phenylmethyl)benzenepropanamide (1.21 g), in MeOH (10 mL) was treated sequentially with molecular sieves 3A (0.5 g), 4-phenyl-4-hydroxypiperidine HCl (0.92 g) and $NaBH_3CN$ (0.88 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. $NaHCO_3$ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (100 mL) The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (0.77 g). Mass spectrum (CI): 525.

Example 34

1-[3-(3,4-Dichlorophenyl)-5-[methyl(phenylmethyl)amino]pentyl]-4-phenyl-4-piperidinol

The title compound was prepared from β -(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl -N-(phenylmethyl)-1-piperidine pentamide following the procedure of Example 2. Mass spectrum (FAB): 511.4.

Example 35

2-[3-(3,4-Dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline

Step A β -(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-isoquinolinepentanoic acid.

3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH_2Cl_2 (300 mL) at 0°C was treated sequentially with 1,2,3,4-tetrahydroisoquinoline (6.0 mL), triethylamine (6.7 mL) and DMAP (472 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with 1N HCl (1 x 200 mL) and water (1 x 200 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (14 g).

Step B 2-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline

β-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-*delta*-oxo-isoquinolinepentanoic acid, (14 g) in EtOAc (300 mL) was treated with CDI (7.25 g) and DMAP (440 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (6.7 g) in H_2O (150 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (500 mL) and washed with 1N HCl (1 x 200 mL), sat. $NaHCO_3$ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (12.4 g). Mass spectrum (CI): 378.

Step C 2-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroisoquinoline

A solution of oxalyl chloride (0.460 mL) in CH_2Cl_2 (20 mL) was cooled to -78°C whereupon DMSO (0.749 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH_2Cl_2 (10 mL) solution of 2-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline (1.0 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et_3N (3 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH_2Cl_2 (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO3 (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 5-15% EtOAc/Hex gave the title compound (800 mg).

Step D 2-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1,2,3,4-tetrahydroisoquinoline

2-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1,2,3,4-tetrahydroisoquinoline (800 mg), in MeOH/THF (1:1, 20 mL) was treated sequentially with molecular sieves 3A (900 mg), 4-phenyl-4-hydroxypiperidine HCl (900 mg) and $NaBH_3CN$ (130 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (810 mg). Mass spectrum (FAB): 537.2075.

Example 36

β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β -[2-[[(3-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid
3-(3,4-Dichlorophenyl)glutaric anhydride (6.7 g) in CH_2Cl_2 (100 mL) at 0°C was treated sequentially with N-methyl-N-[3-methoxyphenyl)methyl]amine (4.7 g), triethylamine (3.27 g) and DMAP (0.32)). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (75 mL) and water (2X75 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (10.5 g).

Step B 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-[(3-methoxyphenyl)methyl]benzenepropanamide
3,4-Dichloro-β -[2-[[(3-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (10.5 g) in EtOAc (150 mL) was treated with CDI (6.22 g) and DMAP (0.3 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (6.3 g) in H_2O (75 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL) , H_2O (250 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude oil (13 g). Silica gel chromatography eluting with 5% MeOH/CH_2Cl_2 gave the title compound (9.35 g).

Step C 3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-[(3-methoxyphenyl)methyl]benzenepropanamide
Oxalyl chloride (3.23 g) in CH_2Cl_2 (100 mL) was added to a -78°C solution of DMSO (4.14 g) in CH_2Cl_2 (20 mL) over 15 mins. This mixture was stirred for 15 minutes whereupon a CH_2Cl_2 (30 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-[(3-methoxyphenyl)methyl] benzenepropanamide (8.4 g) was added dropwise. The mixture was stirred for 30 minutes and then treated with a solution of Et_3N (6.43 g) in CH_2Cl_2 (30 mL) and stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature. The reaction mixture was

washed with water (100 mL), the organic fraction separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil (11 g). Silica gel chromatography eluting with 10% EtOAc/CH_2Cl_2 gave the title compound (7.75 g).

Step D β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(3-methoxyphenyl)methyl] benzenepropanamide (1.23 g), in MeOH (100 mL) was treated sequentially with molecular sieves 3A (4 g), 4-phenyl-4-hydroxypiperidine HCl (0.87 g) and $NaBH_3CN$ (0.83 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. $NaHCO_3$ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (100 mL) The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give an oil (1.8 g). Silica gel chromatography eluting with 5% MeOH/CH_2Cl_2 gave the title compound (0.77 g). Mass spectrum (FAB): 555.

Example 37

1-[3-(3,4-Dichlorophenyl)-5-[[3(methoxyphenyl)methyl]methylamino] pentyl]-4-phenyl-4-piperidinol

The title compound was prepared from β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide following the procedure of Example 2. Mass spectrum (FAB): 541.

Example 38

N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[[3,5-*bis*-(trifluoromethyl)phenyl methyl]methylamino]-2-oxoethyl]-benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (3.1 g, Example 1, Step C) in CH_2Cl_2 (50 mL) at 0°C was treated sequentially with 3,5-*bis*-(trifluoromethyl)benzylamine (3.4 g), triethylamine (1.83 mL) and DMAP (150 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with 1N HCl (1 x 100 mL) and water (1 x 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (6.1 g).

Step B N-[[3,5-*bis*-(trifluoromethyl)phenyl]methyl]-3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-benzenepropanamide
3,4-Dichloro-β-[2-[[3,5-*bis*-(trifluoromethyl)phenylmethyl]methylamino]-2-oxoethyl]-benzenepropanoic acid (6.1 g) in EtOAc (75 mL) was treated with CDI (2.43 g) and DMAP (150 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (1.8 g) in H_2O (30 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (150 mL) and washed with 1N HCl (1 x 100 mL), sat. $NaHCO_3$ (1 x 100 mL) and water (1 x 100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (5.7 g). Mass spectrum (FAB): 502.0791.

Step C N-[3,5-*bis*-(trifluoromethyl)phenylmethyl]-3,4-dichloro-β-(2-oxoethyl)-N-methyl-benzenepropamide
A mixture of N-[[3,5-*bis*-(trifluoromethyl)phenyl]methyl]-3,4-dichloro-β-(2-hydroxyethyl) -N-methyl-benzenepropanamide (1.0 g) and molecular sieves (4Á, 460 mg) in CH_2Cl_2 (20 mL) and was treated with TPAP (36 mg) and 4-methylmorpholine-N-oxide (460 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressur to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (615 mg).

Step D N-[[3,5-*bis*-(trifluoromethyl)phenyl]methyl]-β-(3,4-dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide N-(3,5-*bis*-trifluoromethylphenyl)-3,4-dichloro-β -(2-oxoethyl)-N-methyl-benzenepropamide (615 mg), in MeOH/THF (1:1, 15 mL) was treated sequentially with molecular sieves 3A (525 mg), 4-phenyl-4-hydroxypiperidine HCl (525 mg) and $NaBH_3CN$ (104 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (500 mg). Mass spectrum (FAB): 661.1811.

Example 39

β -(3,4-Dichlorophenyl)-N-[(3,5-dimethoxyphenyl)methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β -[2-[[(3,5-dimethoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (6.45 g) in CH_2Cl_2 (60 mL) at 0°C was treated sequentially with N-methyl-N-[3,5-dimethoxyphenyl)methyl]amine (5.4 g), triethylamine (3.14 g) and DMAP (0.3 g)). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (100 mL) and water (2X100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (11.0 g).

Step B 3,4-Dichloro-β -(2-hydroxyethyl)-N-methyl-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide

3,4-Dichloro-β -[2-[[(3,5-dimethoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (11.0 g) in EtOAc (150 mL) was treated

with CDI (6.08 g) and DMAP (0.3 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (6.2 g) in H_2O (50 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL) , H_2O (250 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude oil (13 g). Silica gel chromatography eluting with 2.5% MeOH/CH_2Cl_2 gave the title compound (9.1 g).

Step C 3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide
Oxalyl chloride (3.2 g) in CH_2Cl_2 (125 mL) was cooled to -78°C and treated with a solution of DMSO (4.12 g) in CH_2Cl_2 (20 mL) over 15 minutes. This mixture was stirred for 15 minutes whereupon a CH_2Cl_2 (30 mL) solution of 3,4-Dichloro-β -(2-hydroxyethyl)-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide (9.0 g) was added dropwise. The mixture was stirred for 30 minutes and then treated with a solution of Et_3N (6.4 g) in CH_2Cl_2 (25 mL) and stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature. The reaction mixture was washed with water (125 mL), the organic fraction separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil (12 g). Silica gel chromatography eluting with 10% EtOAc/CH_2Cl_2 gave the title compound (8.2 g).

Step D β -(3,4-Dichlorophenyl)-N-[(3,5-dimethoxyphenyl)methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide
3,4-Dichloro-β -(2-oxoethyl)-N-methyl-N-[(3,5-dimethoxyphenyl)methyl]benzenepropanamide (1.5 g), in MeOH (75 mL) was treated sequentially with molecular sieves 3A (5 g), 4-phenyl-4-hydroxypiperidine HCl (0.98 g) and $NaBH_3CN$ (0.94 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. $NaHCO_3$ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (100 mL) The organic layer was

separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give an oil (2.1 g). Silica gel chromatography eluting with 5% MeOH/CH_2Cl_2 gave the title compound (1.2 g). Mass spectrum (FAB): 585.

Example 40

β-(3,4-Dichlorophenyl)-N-[(3-fluoro-4-methoxyphenyl)methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[[(3-fluoro-4-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid 3-(3,4-Dichlorophenyl)glutaric anhydride (4.15 g) in CH_2Cl_2 (150 mL) at 0°C was treated sequentially with N-methyl-N-[3-fluoro-4-methoxyphenyl)methyl]amine (3.25 g), triethylamine (2.0 g) and DMAP (0.2)). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (75 mL) and water (2X75 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (7.3 g).

Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-[(3-fluoro-4-methoxyphenyl)methyl]benzenepropanamide 3,4-Dichloro-β-[2-[[(3-fluoro-4-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (7.3 g) in EtOAc (150 mL) was treated with CDI (4.15 g) and N,N-dimethylamino pyridine (0.21 g). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (4.2 g) in H_2O (70 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (250 mL) , H_2O (250 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude oil (12 g). Silica gel chromatography eluting with 2.5% MeOH/CH_2Cl_2 gave the title compound (6.35 g).

Step C 3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(3-methoxyphenyl)methyl]benzenepropanamide Oxalyl chloride (1.44 g) in CH_2Cl_2 (100 mL) was cooled to a -78°C and treated with a solution of DMSO (1.84 g) in CH_2Cl_2 (20 mL) over 15 mins. This mixture was stirred for 15 minutes whereupon a CH_2Cl_2 (30 mL) solution of 3,4-Dichloro-β-(2-hydroxyethyl)-N-[(3-fluoro-4-methoxyphenyl)methyl] benzenepropanamide (3.9 g) was added dropwise. The mixture was stirred for 30 minutes, then treated with a solution of Et_3N (2.85 g) in CH_2Cl_2 (20 mL), then stirred for an additional 30 minutes at -78°C, then allowed to warm to ambient temperature. The reaction mixture was washed with water (100 mL), the organic fraction separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil (5.0 g). Silica gel chromatography eluting with 10% EtOAc/CH_2Cl_2 gave the title compound (3.6 g).

Step D β-(3,4-Dichlorophenyl)-N-[(3-fluoro-4-methoxyphenyl) methyl]-4-hydroxy-N-methyl-4-phenyl-1-piperidinepentamide 3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(3-fluoro-4-methoxyphenyl)methyl]benzenepropanamide (1.05 g), in MeOH (50 mL) was treated sequentially with molecular sieves 3A (3 g), 4-phenyl-4-hydroxypiperidine HCl (0.71 g) and $NaBH_3CN$ (0.67 g). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was treated with satd. $NaHCO_3$ solution (10 mL) and concentrated under reduced pressure. The residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (100 mL). The organic layer was separated and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oil (1.2 g). Silica gel chromatography eluting with 5% MeOH/CH_2Cl_2 gave the title compound (0.92 g). Mass spectrum (FAB): 573.

Example 41

1-[3-(3,4-Dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1H-indole

Step A 3,4-Dichloro-β-[[2-[1-(indolinyl)]]-2-oxoethyl]-benzenepropanoic acid.

3-(3,4-Dichlorophenyl)glutaric anhydride (10 g, Example 1, Step C) in CH_2Cl_2 (150 mL) at 0°C was treated sequentially with indole (5.6 g), triethylamine (6.7 mL) and DMAP (440 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with 1N HCl (1 x 100 mL) and water (1 x 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (14 g).

Step B 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1H-indole 3,4-Dichloro-β-[[2-[1-(indolinyl)]]-2-oxoethyl]-benzenepropanoic acid (14 g) in EtOAc (300 mL) was treated with CDI (12.5 g) and DMAP (470 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for two hours. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (7.3 g) in H_2O (100 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was diluted with EtOAc (300 mL) and washed with 1N HCl (1 x 200 mL), sat. $NaHCO_3$ (1 x 200 mL) and water (1 x 200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude compound as a oil. Silica gel chromatography eluting with 0-10% MeOH/ CH_2Cl_2 gave the title compound (5.5 g)

Step C 1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1H-indole
A mixture of 1-[3-(3,4-dichlorophenyl)-5-hydroxy-1-oxopentyl]-1H-indole (4.25 g) and molecular sieves (4Å, 2.75 g) in CH_2Cl_2 (40 mL) and was treated with TPAP (50 mg) and 4-methylmorpholine-N-oxide (2.75 mg) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a pad of silica gel rinsed with EtOAc (100 mL) and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-75% EtOAc/Hexanes gave the desired title compound (930 mg).

Step D 1-[3-(3,4-dichlorophenyl)-5-(4-hydroxy-4-phenyl-1-piperidinyl)-1-oxopentyl]-1H-indole

1-[3-(3,4-dichlorophenyl)-1,5-dioxopentyl]-1H-indole (740 mg), in MeOH/THF (1:1, 30 mL) was treated sequentially with molecular sieves 3A (880 mg), 4-phenyl-4-hydroxypiperidine HCl (880 mg) and $NaBH_3CN$ (130 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (600 mg). Mass spectrum (CI): 521.

Example 42

β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(2-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[[(2-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (5.9 g) in CH_2Cl_2 (80 mL) at 0°C was treated sequentially with N-methyl-N-[2-methoxyphenyl)methyl]amine (3.8 g), triethylamine (3.5 mL) and DMAP (278 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (1 x 100 mL) and brine (1 x 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (9.3 g).

Step B 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-[(2-methoxyphenyl)methyl]benzenepropanamide

3,4-Dichloro-β-[2-[[(2-methoxyphenyl)methyl]methylamino]-2-oxoethyl]benzenepropanoic acid (9.3 g) in EtOAc (100 mL) was treated with CDI (4.62 g) and DMAP (345 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (3.45 g) in H_2O (50 mL), warmed slowly to room

temperatur and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (1 x 100 mL), H_2O (1 x 100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude oil (13 g). Silica gel chromatography eluting with 5% MeOH/CH_2Cl_2 gave the title compound (8.7 g). Mass spectrum (FAB): 396.1124.

Step C 3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(2-methoxyphenyl) methyl]benzenepropanamide

A solution of oxalyl chloride (1.43 mL) in CH_2Cl_2 (30 mL) was cooled to -78°C whereupon DMSO (2.32 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH_2Cl_2 (20 mL) solution of 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-[(2-methoxyphenyl)methyl]benzenepropanamide (1.3 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et_3N (9.2 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH_2Cl_2 (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO3 (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-100% EtOAc/Hex gave the title compound (950 mg).

Step D β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(2-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-[(2-methoxyphenyl) methyl]benzenepropanamide (950 mg), in MeOH/THF (30 mL, 1:1) was treated sequentially with molecular sieves 3A (770 mg), 4-phenyl-4-hydroxypiperidine HCl (770 mg) and $NaBH_3CN$ (150 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to

give the crude oil. Silica gel chromatography eluting with 5% MeOH/CH_2Cl_2 gave the title compound (720 mg). Mass spectrum (FAB): 555.2181.

Example 43

β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(2-phenylethyl)-1-piperidinepentamide

Step A 3,4-Dichloro-β-[2-[(2-phenylethyl)methylamino]-2-oxoethyl]benzenepropanoic acid

3-(3,4-Dichlorophenyl)glutaric anhydride (3.4 g) in CH_2Cl_2 (50 mL) at 0°C was treated sequentially with N-methylphenethylamine (2.4 mL), triethylamine (2.3 mL) and DMAP (162 mg). The mixture was stirred at 0°C for two hours then allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was washed with 1N HCl (1 x 100 mL) and brine (1 x 100 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (4.6 g).

Step B

3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide

3-3,4-Dichloro-β-[2-[(2-phenethyl)methylamino]-2-oxoethyl]benzenepropanoic acid (4.6 g) in EtOAc (75 mL) was treated with CDI (2.6 g) and DMAP (162 mg). The resulting solution was stirred at room temperature for 15 minutes and then heated at 50°C for 1 hour. The reaction mixture was cooled to 0°C and treated with a solution of $NaBH_4$ (2.5 g) in H_2O (30 mL), warmed slowly to room temperature and stirred for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with 1N HCl (1 x 100 mL) , H_2O (1 x 100 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude oil (5 g). Silica gel chromatography eluting with 2.5% MeOH/CH_2Cl_2 gave the title compound (3.5 g). Mass spectrum (FAB): 380.1177.

Step C 3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-(2-ph nethyl)-benzenepropanamide

A solution of oxalyl chloride (1.25 mL) in CH_2Cl_2 (25 mL) was cooled to -78°C whereupon DMSO (2.03 mL) was added dropwise over 15 mins. This mixture was stirred for 15 minutes. Whereupon a CH_2Cl_2 (25 mL) solution of 3,4-Dichloro-β-(2-hydroxyethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide (1.1 g) was added over 20 minutes. The mixture was stirred for 30 minutes and then treated with Et_3N (9.2 mL) and stirred for an additional 30 minutes at -78°C, followed by 1.5 hours at room temperature. The reaction mixture was quenched with water and diluted with CH_2Cl_2 (100 mL). The organic fraction was separated, washed sequentially with 1N HCl (1 x 50 mL), sat. NaHCO3 (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield an oil. Silica gel chromatography eluting with 50-100% EtOAc/Hex gave the title compound (900 mg).

Step D β-(3,4-Dichlorophenyl)-4-hydroxy-N-(2-phenethyl)-N-methyl-4-phenyl-1-piperidinepentamide

3,4-Dichloro-β-(2-oxoethyl)-N-methyl-N-(2-phenethyl)-benzenepropanamide (900 mg), in MeOH/THF (30 mL, 1:1) was treated sequentially with molecular sieves 3A (800 mg), 4-phenyl-4-hydroxypiperidine HCl (760 mg) and $NaBH_3CN$ (150 mg). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was with quenched with water (20mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude oil. Silica gel chromatography eluting with 1-2% MeOH/CH_2Cl_2 gave the title compound (680 mg). Mass spectrum (FAB): 539.2222.

The *in vitro* and *in vivo* activity of the compounds of formula I can be determined by the following procedures.

In vitro procedure to identify NK_1 activity

T st compounds ar valuated for their ability to inhibit the activity of the NK_1 agonist Substance P on the isolated guinea pig vas deferens. Freshly cut vas deferens are removed from male Hartley guinea pigs (230-350g) and suspended in 25 ml tissue baths containing Kreb's Henseleit solution warmed to 37°C and constantly aerated with 95% O_2 and 5% CO_2. Tissues are adjusted to 0.5 g and allowed to equilibrate for a period of 30 minutes. The vas deferens are exposed to an electrical field stimulation (Grass S48 Stimulator) every 60 seconds at an intensity that will cause the tissue to contract 80% of its maximum capacity. All responses are recorded isometrically by means of a Grass force displacement transducer (FT03) and Harvard electronic recorder. Substance P inhibits the electrical field stimulated-induced contractions of the guinea pig vas deferens. In unpaired studies, all tissues (control or drug treated) are exposed to cumulative concentrations of Substance P ($1X10^{-10}$ M - $7X10^{-7}$ M). Single log-concentrations of the test compounds are given to separate tissues and allowed to equilibrate for 30 minutes before a Substance P concentration-response curve is generated. At least 5 separate tissues are used for each control and individual drug-concentration for every drug assay.

Inhibition of the Substance P is demonstrated by a rightward shift of its concentration-response curve. These shifts are used to determine the pA_2 value, which is defined as the negative log of the molar concentration of the inhibitor which would require that twice as much agonist be used to elicit a chosen response. This value is used to determine relative antagonist potency.

Isolated Hamster Trachea NK_2 Assay

General methodology and characterization of hamster trachea responses to neurokinin agonists as providing an NK_2 monoreceptor assay is found in C.A. Maggi, et al., *Eur. J. Pharmacol.* 166 (1989) 435 and J.L. Ellis, et al., *J. Pharm. Exp. Ther.* 267 (1993) 95.

Continuous isometric tension monitoring is achieved with Grass FT-03 force displacement transducers connected to Buxco Electronics preamplifiers built into a Graphtec Linearcorder Model WR 3310.

Male Charles River LAK:LVG (SYR) hamsters, 100-200 g fed weight, are stunned by a sharp blow to the head, loss of corneal reflex is assured, the hamsters are sacrificed by thoractomy and cutting the heart. Cervical trachea segments are removed to room temperature Krebs buffer, pH 7.4, aerated with 95% O_2 - 5% CO_2 gas and cleaned of adhering tissue. The segments are cut into two 3-4 mm long ring segments. Tracheal rings are suspended from transducers and anchored in 15.0 ml water jacketed organ baths by means of stainless steel hooks and 6-0 silk. Baths are filled with Krebs buffer, pH 7.4, maintained at 37°C and continuously aerated with 95% O_2 - 5% CO_2 gas. Tracheal rings are placed under 1.0 g initial tension and allowed a 90 min equilibration period with four 1 µM NKA challenge, wash and recovery cycles at 20 min intervals. 30 min vehicle pretreatment is followed by cumulative additions of rising doses of NKA (3 nM - 1 µM final concentration, 5 min intervals between additions). The final NKA response is followed by a 15 min wash and recovery period. 30 min pretreatment with a test compound or its vehicle is followed by cumulative additions of rising doses of NKA (3 nM - 10 µM final concentration if necessary, 5 min intervals between additions). The final NKA response is followed by a 1 mM carbachol challenge to obtain a maximal tension response in each tissue.

Tissue responses to NKA are recorded as positive pen displacements over baseline and converted to grams tension by comparison to standard weights. Responses are normalized as a % of the maximal tissue tension. ED_{50}'s are calculated for NKA from the control and treated NKA dose responses and compared. Test compounds resulting in an agonist dose ratio ≥ 2 at a screening concentration of 1 µM (i.e. $pA_{2 \geq} = 6.0$) are considered actives. Further dose response data is obtained for actives so that an apparent pA_2 estimate can be calculated. pA_2 is calculated either by estimation of K_i as described by Furchgott (where $pA_2 = -\text{Log } K_i$, R.F. Furchgott, *Pharm. Rev.* 7 [1995] 183) or by Shild Plot Analysis (O. Arunlakshana & H.O. Shild, *Br. J. Pharmacol.* 14[1959] 48) if the data is sufficient.

Effect of NK_1 Antagonists on Substance P-Induced Airway Microvascular Leakage in Guinea Pigs

Studies are performed on male Hartley guinea pigs ranging in weight from 400-650 g. The animals are given food and water *ad libitum*. The animals are anesthetized by intraperitoneal injection of dialurethane (containing 0.1 g/ml diallylbarbituric acid, 0.4 g/ml ethylurea and 0.4 g/ml urethane). The trachea is cannulated just below the larynx and the animals are ventilated (V_T = 4 ml, f = 45 breaths/min) with a Harvard rodent respirator. The jugular vein is cannulated for the injection of drugs.

The Evans blue dye technique (Danko, G. et al., Pharmacol. Commun., 1, 203-209, 1992) is used to measure airway microvascular leakage (AML). Evans blue (30 mg/kg) is injected intravenously, followed 1 min later by i.v. injection of substance P (10 µg/kg). Five min later, the thorax is opened and a blunt-ended 13-gauge needle passed into the aorta. An incision is made in the right atrium and blood is expelled by flushing 100 ml of saline through the aortic catheter. The lungs and trachea are removed en-bloc and the trachea and bronchi are then blotted dry with filter paper and weighed. Evans blue is extracted by incubation of the tissue at 37°C for 18 hr in 2 ml of formamide in stoppered tubes. The absorbance of the formamide extracts of dye is measured at 620 nm. The amount of dye is calculated by interpolation from a standard curve of Evans blue in the range 0.5-10 µg/ml in formamide. The dye concentration is expressed as ng dye per mg tissue wet weight. Test compounds were suspended in cyclodextran vehicle and given i.v. 5 min before substance P.

Measurement of NK_2 Activity In Vivo

Male Hartley guinea pigs (400-500 gm) with ad lib. access to food and water are anesthetized with an intraperitoneal injection of 0.9 ml/kg dialurethane (containing 0.1 g/m diallylbarbituric acid, 0.4 g/ml ethylurea and 0.4 g/ml urethane). After induction of a surgical plane of anesthesia, tracheal, esophageal and jugular venous cannulae are implanted to facilitate mechanical respiration, m asurement of esophageal pressure and administration of drugs, respectively.

The guinea pigs are placed inside a whole body plethysmograph and the catheters connected to outlet ports in the plethysmograph wall. Airflow is measured using a differential pressure transducer (Validyne, Northridge CA, model MP45-1, range ± 2 cmH_2O) which measures the pressure across a wire mesh screen that covers a 1 inch hole in the wall of the plethysmograph. The airflow signal is electrically integrated to a signal proportional to volume. Transpulmonary pressure is measured as the pressure difference between the trachea and the esophagus using a differential pressure transducer (Validyne, Northridge, CA, model MP45-1, range ± 20 cm H_2O). The volume, airflow and transpulmonary pressure signals are monitored by means of a pulmonary analysis computer (Buxco Electronics, Sharon, CT, model 6) and used for the derivation of pulmonary resistance (R_L) and dynamic lung compliance (C_{Dyn}).

Bronchoconstriction Due to NKA

Increasing iv doses of NKA are administered at half log (0.01-3 µg/kg) intervals allowing recovery to baseline pulmonary mechanics between each dose. Peak bronchoconstriction occurs within 30 seconds after each dose of agonist. The dose response is stopped when C_{Dyn} is reduced 80-90% from baseline. One dose-response to NKA is performed in each animal. Test compounds are suspended in cyclodextran vehicle and given i.v. 5 min before the initiation of the NKA dose response.

For each animal, dose response curves to NKA are constructed by plotting the percent increase in R_L or decrease in C_{Dyn} against log dose of agonist. The doses of NKA that increased R_L by 100% (R_L100) or decreased C_{Dyn} by 40% ($C_{Dyn}40$) from baseline values are obtained by log-linear interpolation of the dose response curves.

Neurokinin Receptor Binding Assay(s)

Chinese Hamster ovary (CHO) cells transfected with the coding regions for the human neurokinin 1 (NK_1) of the human neurokinin 2 (NK_2) receptors are grown in Dulbecco's minimal essential

medium supplemented with 10% fetal calf serum, 0.1 mM non-essential amino acids, 2 mM glutamine, 100 units/ml of penicillin and streptomycin, and 0.8 mg of G418/ml at 37°C in a humidified atmosphere containing 5% CO_2.

Cells are detached from T-175 flasks with a sterile solution containing 5 mM EDTA in phosphate buffered saline. Cells are harvested by centrifugation and washed in RPMI media at 40°C for 5 minutes. The pellet is resuspended inTris-HCl (pH7.4) containing 1 uM phsphoramidon and 4 ug/ml of chymostatin at a cell density of 30 x 10^3 cells/ml. The suspension is then homogenized in a Brinkman Polytron (setting 5) for 30-45 seconds. The homogenate is centrifuged at 800 x g for 5 min at 4°C to collect unbroken cells and nuclei. The supernatant is centrifuged in a Sorvall RC5C at 19,000 rpm (44,00 x g) for 30 min at 4°C. The pellet is resuspended, an aliquot is removed for a protein determination (BCA) and washed again. The resulting pellet is stored at -80°C.

To assay receptor binding, 50 µl of [^{3}H]-Substance P (9-Sar, 11-Met [02]) (specific activity 41 Ci/mmol) (Dupont-NEN) (0.8 nM for the NK-1 assay) or [^{3}H]-Neurokinin A (specific activity 114 Ci/ mmole) (Zenca) (1.0 nM for the NK-2 assay) is added to tubes containing buffer (50 mM Tris-HCl (pH 7.4) with 1 mM $MnCl_2$ and 0.2% Bovine Serum Albumin) and either DMSO or test compound. Binding is initiated by the addition of 100µl of membrane (10-20 µg) containing the human NK-1 or NK-2 receptor in a final volume of 200 µl. After 40 minutes at room temperature, the reaction is stopped by rapid filtration onto Whatman GF/C filters which have been presoaked in 0.3% polyethylenimine. Filters are washed 2 times with 3 ml of 50 mM Tris-HCl (pH7.4). Filters are added to 6 mls of Ready-Safe liquid scintillation cocktail and quantified by liquid scintillation spectrometry in a LKB 1219 RackBeta counter. Non-specific binding is determined by the addition of either 1 µM of CP-99994 (NK_1) or 1µM SR-48968 (NK_2) (both synthesized by the chemistry department of Schering-Plough Research Institute). IC_{50} values are determined from competition binding curves and Ki values are determined according to Cheng and Prusoff using the

experimentally determined value of 0.8 nM for the NK_1 receptor and 2.4 nM for the NK_2 receptor.

Using the test procedures described above, the following data were obtained for representative compounds of formula I:

For all of the compounds of the invention, the NK_1 binding is in a range of about 7-97% inhibition at 1 μM concentration. For all of the compounds of the invention, the NK_2 binding is in a range of about 0-90% inhibition at 1 μM concentration. It should be understood that while the NK_2 binding for certain compounds of the invention is as low as 0% at 1 μM concentration, that at higher concentrations these compounds may have NK_2 binding inhibition activity.

Activities of representative compounds of the invention in the above Neurokinin Receptor Binding Assay are as follows:

β -(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-N,4-diphenyl -1-piperidinepentamide

Binding; NK_1 K_i = 150 nM; NK_2 K_i = 5.2 nM.

β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(phenylmethyl)-1-piperidinepentamide

Binding; NK_1 K_i = 6.8 nM; NK_2 K_i = 108 nM.

β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(3-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

Binding; NK_1 K_i = 12 nM; NK_2 K_i = 215 nM.

β-(3,4-Dichlorophenyl)-4-hydroxy-N-[(2-methoxyphenyl)methyl]-N-methyl-4-phenyl-1-piperidinepentamide

Binding; NK_1 K_i = 7.5 nM; NK_2 K_i = 33 nM.

β-(3,4-Dichlorophenyl)-4-hydroxy-N-methyl-4-phenyl-N-(2-phenylethyl)-1-piperidinepentamide

Binding; NK_1 K_i = 70 nM; NK_2 K_i = 46 nM.

The K_i of a compound is that concentration at which the compound caused 50% inhibition of either NK_1 or NK_2. For those compounds of the invention having higher than 50% inhibition of NK_1 , K_i 's for NK_1 were determined. The K_i 's for NK_1 for such compounds fell within a range of about 6.8nM to about 215 nM.

For those compounds of the invention having higher than 50% inhibition of NK_2 , K_i 's for NK_2 were determined. The K_i 's for NK_2 for such compounds fell within a range of about 5.2nM to about 215 nM.

It will be recognized that compounds of formula I exhibit NK_1 and NK_2 antagonist activity to varying degrees, i.e., certain compounds have strong NK_1 antagonist activity, but weaker NK_2 antagonist activity. Others are strong NK_2 antagonists, but weaker NK_1 antagonists. While compounds with approximate equipotency are preferred, it is also within the scope of this invention to use compounds of with unequal NK_1/NK_2 antagonist activity when clinically appropriate.

Compounds of formula I have been found to be antagonists of both NK_1 and NK_2 receptors, and are therefore useful in treating conditions caused or aggravated by the activity of NK_1 and NK_2 receptors.

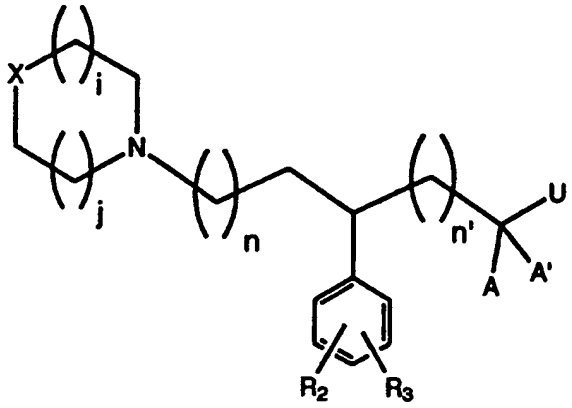
The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. Compounds of this invention can be administered in conventional oral dosage forms such as capsules, tablets, powders, cachets, suspensions or solutions, or in injectable dosage forms such as solutions, suspensions, or powders for reconstitution. The pharmaceutical compositions can be prepared with conventional excipients and additives, using well known formulation techniques. Pharmaceutically acceptable excipients and additives include nontoxic and chemically compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily dose of a compound of formula I for treating asthma, cough, bronchospasm, inflammatory disease, migraine, nociception and gastrointestinal disorders is about 0.1 mg to about 20 mg/kg of body weight per day, preferably about 0.5 to about 15 mg/kg,

more preferably 0.5 to about 5 mg/kg. For an average body weight of 70 kg, the dosage range is therefore from about 1 to about 1500 mg of drug per day, preferably about 50 to about 100 mg , given in a single dose or 2-4 divided doses. The exact dose , however is determined by the attending clinician , and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

WHAT IS CLAIMED IS:

1. The invention relates to compounds of the formula



I

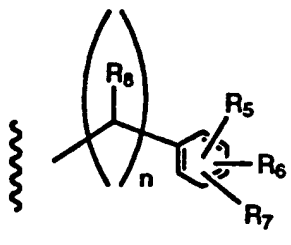
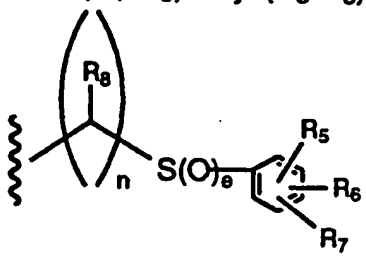
wherein each i and j is independently selected from the group consisting of 1 and 2;

each n is independently selected from the group consisting of 0, 1, 2 and 3; and each n' is independently selected from the group consisting of 1, 2 and 3;

wherein A and A' are H, or A and A' taken together are =O, =S; or =N-R_4;

X is selected from the group consisting O, CO, C(R, R_1), C=C(R_1,R_8), NR_1, and $S(O)_e$ wherein e is 0, 1, or 2;

R is selected from the group consisting of H, OR_8, $CON(R_8)_2$, CN, $S(O)_eR_8$, $SO_eN(R_8)_2$, CO_2R_8, and NR_4COR_8;

R_1 is selected from the group consisting of H, (C_1-C_6)-alkyl (C_3-C_8)-cyclo-alkyl,  , and  ;

R_2, R_3 , R_5, R_6 and R_7 are independently selected from the group consisting of H, halogen, (C_1-C_6)-alkyl, CF_3, C_2F_5, OR_8, COR_8, CO_2R_8, $CON(R_8, R_8)$, $N(R_8, R_8)$, $N(R_8)COR_8$, $S(O)_eR_8$, $OC(O)R_4$, $OC(O)N(R_8, R_4)$, $NR_8CO_2R_4$, $NR_8(CO)N(R_8,R_8)$, R_{15}-phenyl, R_{15}-benzyl, NO_2,

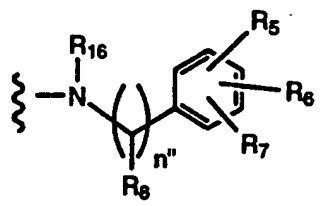
$NR_8SO_2R_4$, $-S(O)_2N(R_8)_2$ or when R_2 and R_3 or any two of R_5, R_6 and R_7 are on adjacent carbons they may form a $-O-CH_2-O-$ group;

each R_4 is independently selected from the group consisting of alkyl, substituted alkyl, substituted aryl, and substituted benzyl;

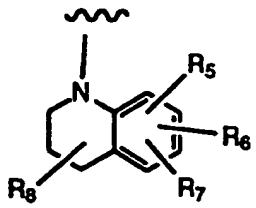
each R_8 is independently selected from the group consisting of H, alkyl, substituted alkyl, substituted aryl, and substituted benzyl;

each R_{15} is independently H, halogen, lower alkyl, lower alkoxy; and

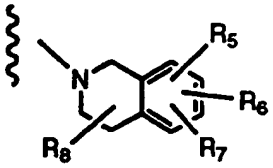
U is



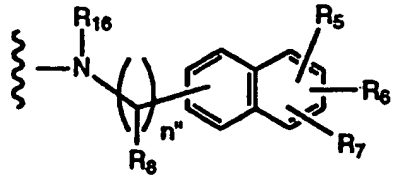
(A)



(B)

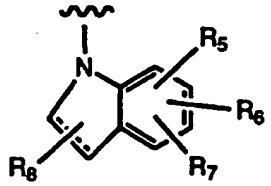


(C)



(D)

,or



(E)

n" is independently selected from the group consisting of 0, 1, 2 and 3;

the dashed line is an optional carbon-carbon bond;

R_{16} is H, (C_1-C_6)-alkyl, $-S(O)_2R_4$, COR_8, CO_2R_4 where R_4 is not H, $CON(R_8)_2$, R_{15}-phenyl or R_{15}-benzyl;

substituted means substituted with a substituent selected from the group consisting of H, (C_1-C_6) alkyl, OCF_3, CF_3, and C_2F_5.

2. A compound according to claim 1, wherein i is 1 and j is 1.

3. A compound according to claim 1, wherein n is 1, n" is 0, 1, or 2, and n' is 1.

4. A compound according to claim 1, wherein n, n', and n" are all 1.

5. A compound according to claim 1, wherein n, and n' are both 1, and n" is 0.

6. A compound according to claim 1, wherein n, and n' are both 1, and n" is 2.

7. A compound according to claim 1, wherein A and A' are both H

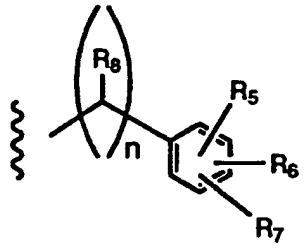
8. A compound according to claim 1, wherein A and A' taken together are =O.

9. A compound according to claim 1, wherein X is C(R, R_1).

10. A compound according to claim 1, wherein R is OR_8, $CON(R_8)_2$ CN, or NR_4COR_4.

11. A compound according to claim 1, wherein X is NR_1 .

12. A compound according to claim 1, wherein R_1 is



13. A compound according to claim 10, where n is 0 or 1 and R_8 is H.

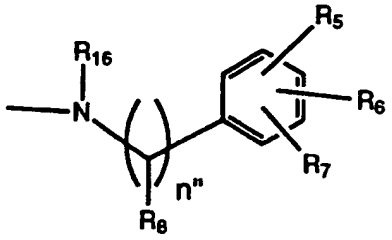
14. A compound according to claim 10, wherein R_2, R_3, R_5, R_6 and R_7 are H, halogen, C_1-C_6 alkyl, CF_3, OR_8, COR_8, CO_2R_8, $CONR_8,R_8$, or NR_8,R_8.

15. A compound according to claim 10, wherein R_{16} is H or alkyl.

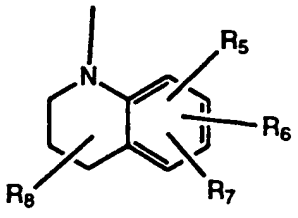
16. A compound according to claim 10, wherein each R_8 is selected from the group consisting of H, C_1-C_6 alkyl, and R_{15}-phenyl .

17. A compound according to claim 10, wherein R_8 is H or substituted alkyl.

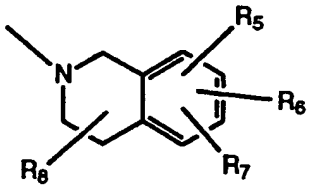
18. A compound according to claim 10, wherein U is



(A)

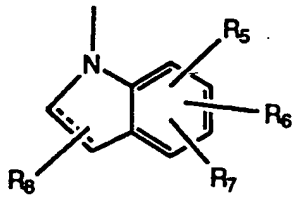


(B)



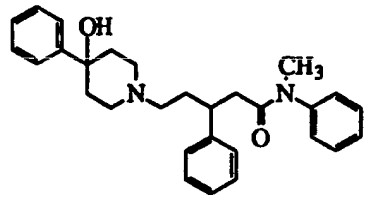
(C)

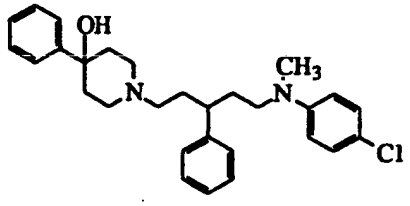
, or

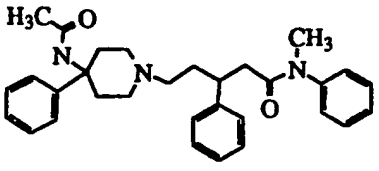


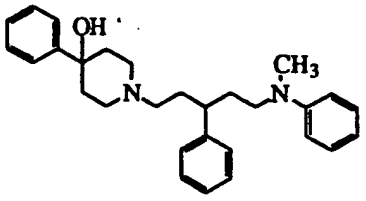
(D)

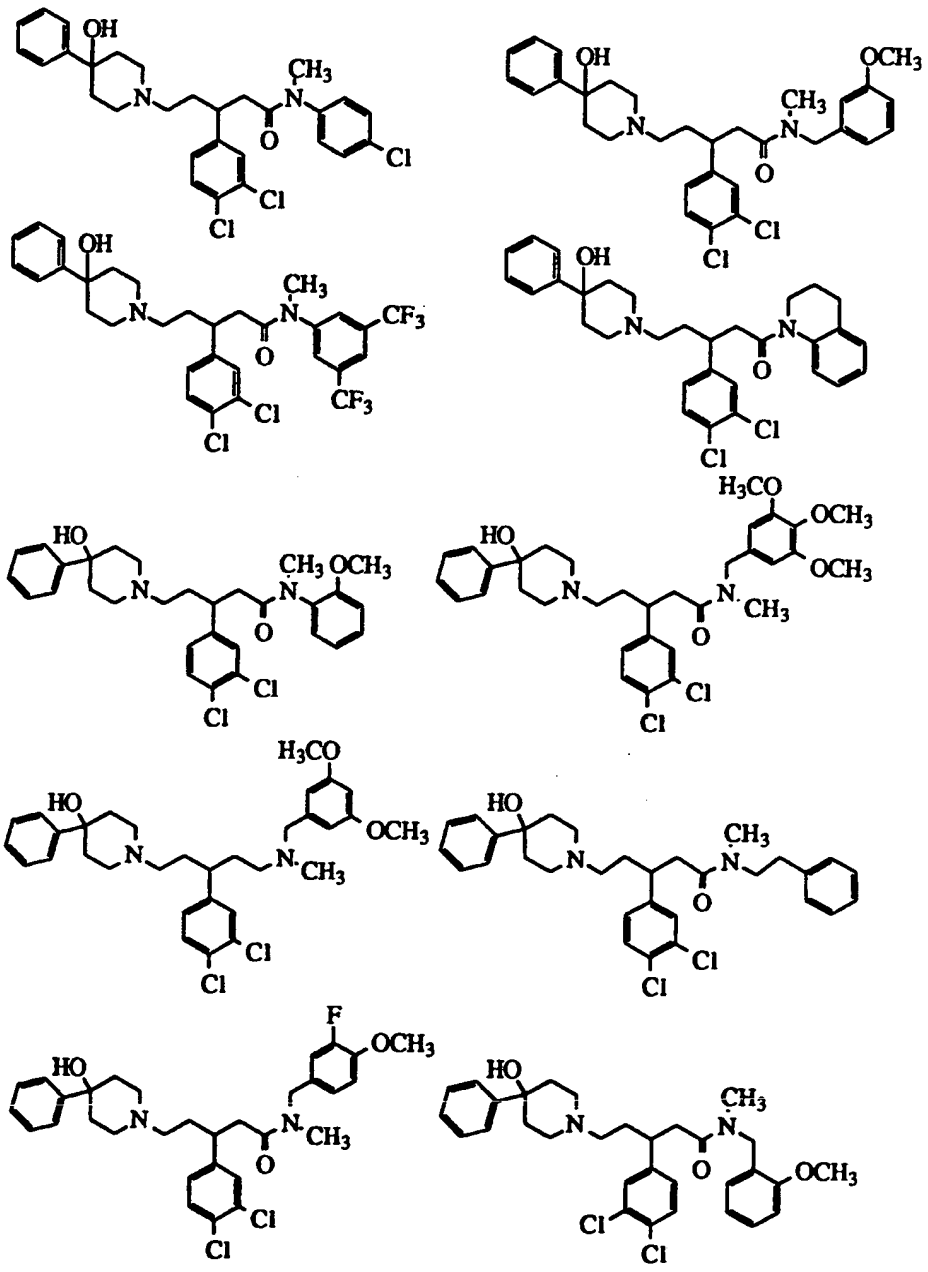
19. A compound according to claim 1, selected from the group consisting of

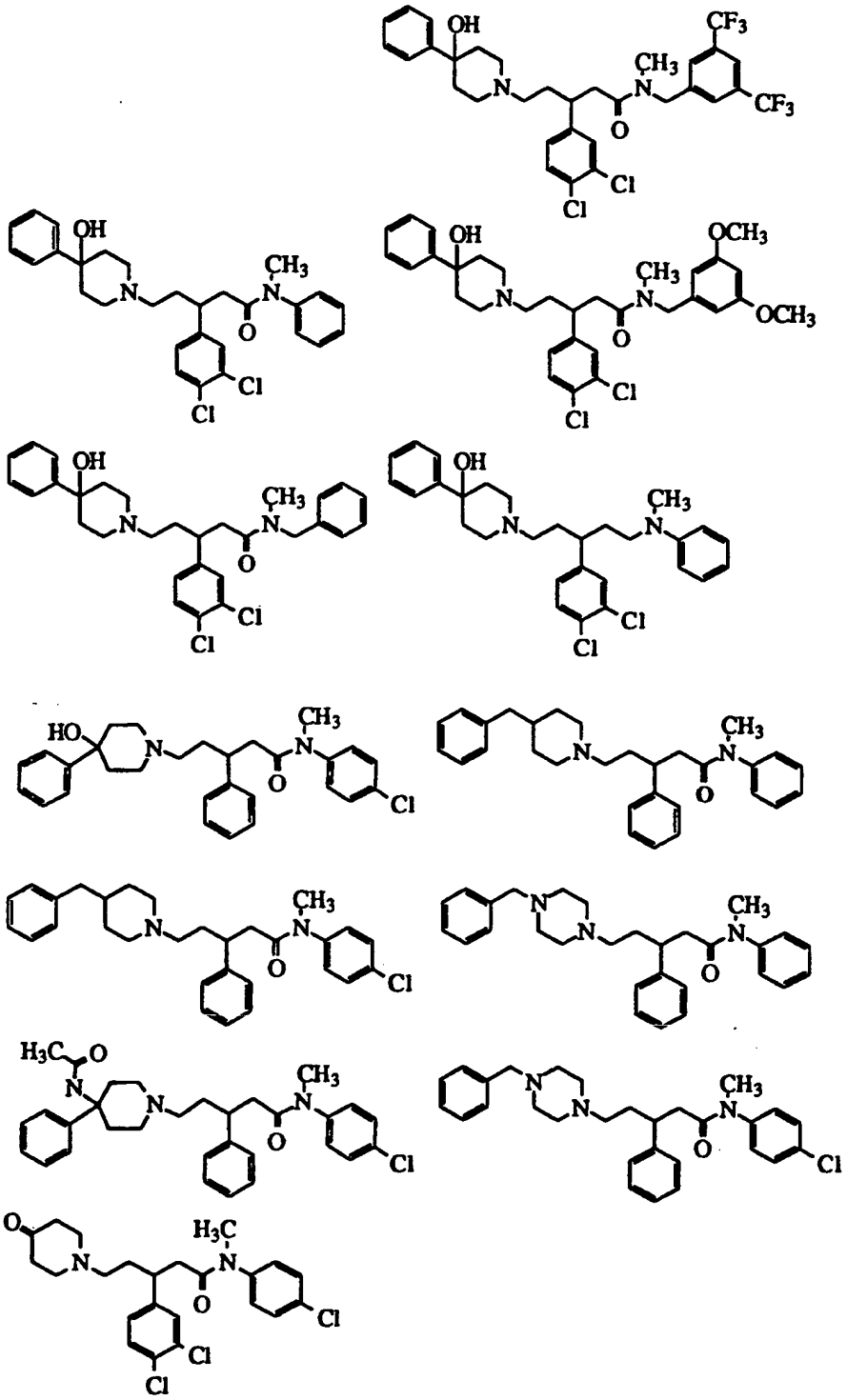












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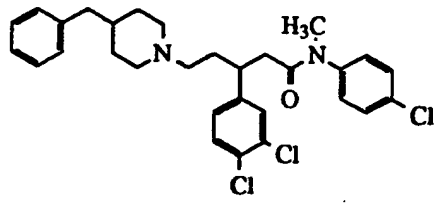

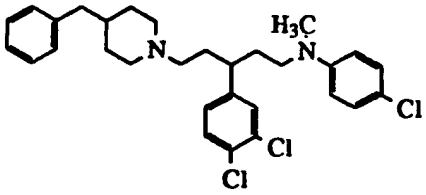

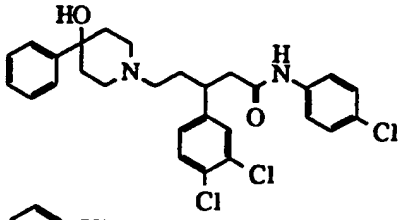

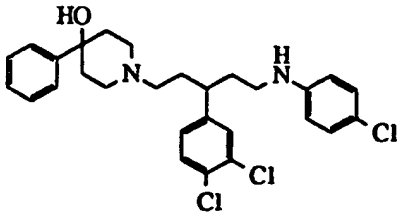

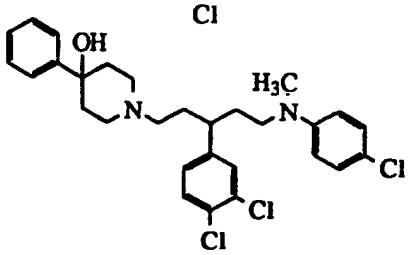

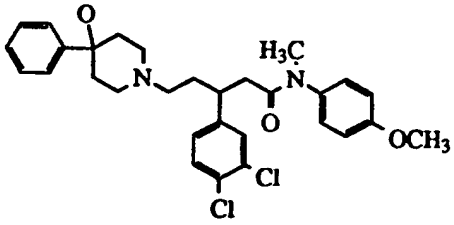

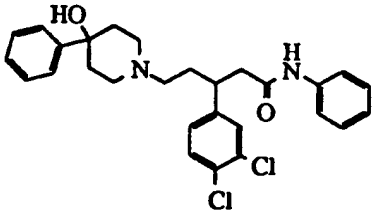

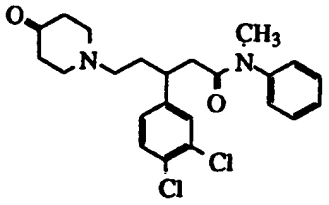

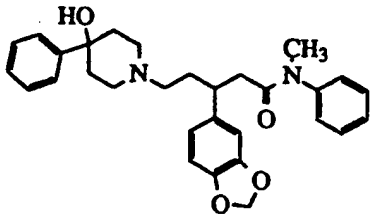

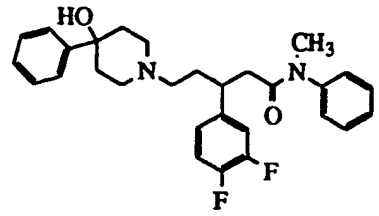

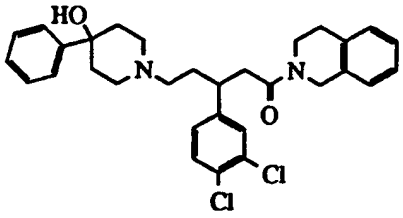

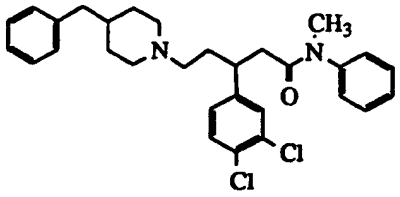

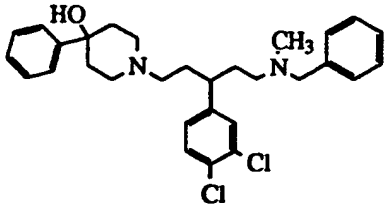

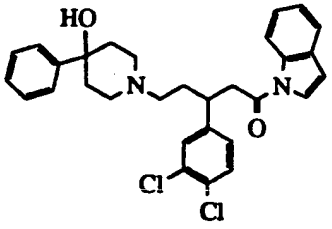

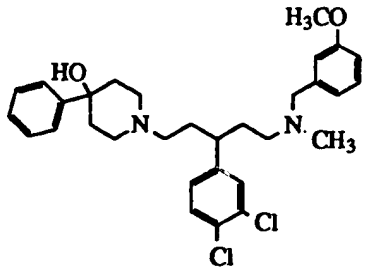

or a pharmaceutically acceptable salt thereof.

20. A composition comprising a neurokinin antagonistic effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier material.

21. A method for inducing neurokin antagonism which comprises administering a neurokinin antagonistic effective amount of a compound according to claim 1 to a mammal in need thereof.

22. A method for treating chronic airway diseases such as asthma and allergies; inflammatory diseases such as inflammatory bowel disease, psoriasis, osteoarthritis, and rheumatoid arthritis; migraine; central nervous system disorders such as depression, psychosis, dementia, and Alzheimer's disease; Down's syndrome; neuropathy; multiple sclerosis; ophthalmic disorders; conjunctivitis; auto immune disorders; graft rejection; systemic lupus erythematosus; GI disorders such as Crohn's disease and ulcerative colitis; disorders of bladder function; circulatory disorders such as angina; Raynaud's disease; coughing and pain which comprises administering a neurokinin antagonistic effective amount of a compound according to claim 1 to a mammal in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/07959

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/14 C07D211/52 C07D211/58 C07D295/14 C07D211/74
C07D405/06 C07D401/06 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 29309 (MERCK AND CO., INC., USA) 22 December 1994 see the whole document ---	1-22
A	WO,A,93 25527 (LUNDBECK, H., A/S, DEN.) 23 December 1993 see abstract ---	1-19
A	GB,A,1 103 524 (INSTITUTO DE ANGELI S.P.A.) 14 February 1968 see the whole document ---	1-22
A	EP,A,0 428 434 (SANOFI SA) 22 May 1991 see the whole document --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 1996	16.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Kissler, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/07959

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO,A,95 26335 (SANOFI SA ;EMONDS ALT XAVIER (FR); PROIETTO VINCENZO (FR); BROECK) 5 October 1995 see the whole document	1-22
A	EP,A,0 474 561 (SANOFI SA) 11 March 1992 see the whole document	1-22
A	EP,A,0 630 887 (ZENECA LTD) 28 December 1994 see the whole document	1-22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ıational application No.

PCT/US96/07959

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21 and 22 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION C NTINUED FR M PCT/ISA/

Claims 1-18, 20-22 have been searched incompletely.

Obscurity

The generic formula I contains almost no fixed structural moiety. In addition, the large number of values for most of the variables, in conjunction with their cascading meanings, renders the scope of the invention for which protection is sought ill-defined and obscure. Consequently, a complete search is precluded for practical and economic reasons.

Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

X=N,C, i=j=1, n=n'=1, A and A' are CO, CH2,

(Cf. Arts. 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/US 96/07959

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9429309	22-12-94	AU-B-	7201194	03-01-95
		CA-A-	2163995	22-12-94
		EP-A-	0702681	27-03-96
		ZA-A-	9403946	20-01-95
WO-A-9325527	23-12-93	AU-B-	4311393	04-01-94
		CA-A-	2137811	23-12-93
		CZ-A-	9403122	13-09-95
		EP-A-	0649407	26-04-95
		FI-A-	945808	09-12-94
		JP-T-	8503690	23-04-96
		NO-A-	944757	31-01-95
		SK-A-	152694	10-05-95
		ZA-A-	9304031	07-01-94
GB-A-1103524		BE-A-	693789	08-08-67
		FR-M-	6578	30-12-68
		FR-A-	1511281	08-04-68
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